Abdominal Solid Organ Transplantation

Immunology, Indications, Techniques, and Early Complications

Antonio Daniele Pinna
Giorgio Ercolani *Editors*

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Preface

Since 1963, when Thomas E. Strarzl performed the first human liver transplantation in a baby, a long way has been passed in the field of solid organ transplantation. Improvements in the surgical techniques and in immunosuppression in the early years not always achieved the expected results, and outcome was more often measured in months rather than years. In the late 1980s, a dramatic improvement in the patient's management and the discoveries of new immunosuppressive drugs led the shifting of organ transplantation from an experimental procedure to a real treatment that could have been offered to a larger proportion of patients affected by end-stage acute or chronic organ failures.

From those years, the clinical and scientific interest in organ transplantation has broadened, involving ethical issues, transplant infectious disease, critical care management, and new strategies to increase the donor pool. Furthermore, because post-transplant outcome is now measured in terms of years and decades, new clinical issues have been raised, like management of metabolic disease or viral reinfection or neoplastic disease, either recurrence or de novo.

Under the incentive of my active associate Giorgio Ercolani, we decided to try to summarize in a single book the new immunological strategies, the surgical innovative techniques, risks of infections after transplantation with a look to potential transmission from donors and innovative transplant procedures. We have asked my friend Dr. Alessandro Nanni Costa, President of the Italian Transplant Network, to report the Italian Guidelines in the evaluation and management of potential donors. We have then tried to focus on peculiar aspects of transplantation of liver, kidney, and small bowel underlining the indications, the technical aspects with special attention to living donor transplantation and the diagnosis and the management of the complications. Finally, two separate chapters are dedicated to the most frequently combined abdominal solid organ transplants (liver-kidney and kidney-pancreas).

I would like to thank all the contributors for the excellent work they have done, and I believe that this book might be useful for all physicians and surgeons involved in this field.

Bologna, Italy — Antonio D. Pinna, MD

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Transplantation Immunology

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Mihir M. Shah*, Naftali Presser*, and John J. Fung

1.1 Introduction

The twentieth century began with uniformly unsuccessful endeavors at investigational allotransplantation, and the next half-century was marked by repeated failure. The recognition of histocompatibility antigens [1] and the primary role of lymphocytes [2] in allorecognition were the two innovations that laid the foundation of transplant immunology that was to eventually form the basis for strategies leading to successful solid organ transplantation.

In the era preceding the development of dialysis, where end-stage renal disease meant imminent death, numerous attempts at renal transplantation failed to yield long-term survivors. The first successful renal transplant, performed between identical twins at the Peter Bent Brigham Hospital in Boston on December 23, 1954, by Moore, Murray, Merrill, and Harrison, energized the transplant community with passion – the barrier of histoincompatibility overcome by virtue of transplantation of a kidney between identical twins, nevertheless demonstrating the utility of organ replacement. Subsequently, Starzl performed the first successful kidney transplant between histoincompatible individuals, under azathioprine-based immunosuppression, 6 years following the twin transplant [3].

"The Relation of Immunology to Tissue Homotransplantation" was the title for the first international transplant conference sponsored by the New York Academy of

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Sciences in 1954 [4]. Current strategies in solid organ transplantation are based upon a comprehensive understanding of immunology and the use of potent immunosuppressive agents, which have led to high rates of success. Investigations in transplantation immunology have led to paradigm shifts in immunology and have greatly contributed to novel approaches to enhance allograft survival while minimizing morbidity.

In this chapter, we will provide an overview of transplant immunology including the principles of allorecognition, the immunological basis of organ rejection (including the immunology of xenotransplantation), and the rationale for historical and current immunosuppressive therapy. Focus will be placed on clinical solid organ transplantation with emphasis on fundamental concepts related to the up-to-date practice of transplant medicine.

1.2 Allorecognition

1.2.1 Major Histocompatibility Complex

The major histocompatibility complex (MHC) refers to a collection of genes, or genetic region, whose fundamental function is the production of proteins that present self and foreign antigens (peptide fragments) to immunocytes as part of normal immunologic surveillance. These complexes of peptide fragments in conjunction with MHC molecules are recognized by specific receptors on immunocytes and under specific circumstances initiate an immunologic cascade with the intent of creating a regulated and targeted response.

Human leukocyte antigen (HLA) is the term used for human MHC molecules. Two distinct classes of MHC antigens, Class I (HLA-A, HLA-B, HLA-C) and Class II (HLA-DR, HLA-DP, HLA-DQ), are located on chromosome 6. HLA Class I molecules are expressed on all nucleated cells as well as platelets, while HLA Class II are associated with antigen-presenting cells (APCs), including lymphocytes, monocytes, macrophages, and dendritic cells. A limiting factor in the exchange of organs between nonidentical individuals is the high degree of polymorphisms within the HLA loci, with resultant large numbers of allelic combinations resulting in low probabilities of complete matching in a random setting. The difference in MHC molecules between the donor and recipient is a primary cause of graft rejection.

1.2.2 Mechanisms of Allorecognition

In the thymus, T lymphocytes are selected for their ability to differentiate self from nonself, i.e., those T lymphocytes with excessive affinity for self-MHC are deleted (negative selection), whereas those with appropriate affinity are designated for maturation and export to the peripheral immune system (positive selection). This process is designed to deal with altered self (both viral- and tumor-related changes) as well as foreign antigens from bacterial and parasitic infections. Physiologic antigen processing involves peptide fragment generation via proteasome degradation of

cytosolic proteins and presentation on Class I MHC and via proteolytic degradation of proteins within phagosomes and subsequent presentation with Class II MHC antigens. This process entails indirect antigen presentation, meaning that the immunocyte receptor recognizes the peptide fragments in context within the MHC binding groove.

Conceptually, the immune system would never naturally encounter alloantigens – the sole exception being in the context of pregnancy. Although the placenta provides a barrier between the mother and fetus during pregnancy, low levels of maternal and fetal cells can be found circulating in the fetus and the mother, respectively. Persistence of fetal cells in the mother has been associated with late autoimmune disorders [5], while the presence of maternal cells in the fetus is associated with tolerance to maternal antigens [6] and may also be associated with autoimmune disorders in offspring [7]. Since all pregnant women have detectable fetal cells in their blood by 36 weeks of gestation, elimination of these cells may be mediated by peripherally circulating T cells with high affinity for nonself HLA and would entail direct allorecognition rather than generating alloantibody responses through indirect antigen presentation, which may adversely affect subsequent pregnancies.

In allotransplantation, recognition of foreign MHC likely involves both indirect and direct allorecognition. Indirect allorecognition utilizes a mechanism similar to the one involved in recognition of foreign antigens – specifically, fragments of foreign MHC molecules are processed through the phagosome and presented as antigenic peptides bound in the groove of self-MHC Class II molecules on APC. In direct allorecognition, foreign MHC molecules on donor cells that migrate out of the allograft are directly recognized by T lymphocytes, perhaps secondary to the innate affinity of T-cell receptors (TCR) for MHC molecules [8]. The binding of these TCR in direct antigen presentation is not thought to be specifically to the MHC binding groove; in fact, the recognition of donor MHC does not require antigen processing through APC [9].

It is possible that the direct allorecognition pathway predominates in the early phases of alloimmune responses and accounts for the strength of the alloimmune response related to a high T-cell precursor frequency, estimated to be as high as one in ten circulating T cells. It has been speculated that indirect alloantigen presentation may be important in chronic transplant rejection, which is likely to be mediated through various cytokines and chemokines released by T helper cells, as well as the effects of alloantibody generated by B cells stimulated via an indirect antigen presentation pathway.

1.2.3 Transplant Rejection

1.2.3.1 Hyperacute Rejection

Patients, who have had prior exposure to MHC antigens via previous transplant procedures, blood transfusions, or pregnancies, are at risk for developing antibodies reactive with alloantigens. When preexisting antibodies to blood groups, HLA, or other polymorphic antigens expressed on the graft are present in the recipient, they

can immediately bind to the graft and activate complement or arm cytolytic cells via antibody-dependent cellular cytotoxicity (ADCC) pathways. When the B-cell surface immunoglobulin receptor binds specific noncarbohydrate antigens in the context of soluble T helper cytokines, B cells are activated. CD4+ helper T-cell cytokines are responsible for the activation of B cells and thus indirectly for the majority of antibody production. B cells undergo differentiation, divide, and become plasma cells, which secrete soluble forms of the antigen-specific antibodies displayed on their cell surface. Plasma cells are long-lived and migrate to the bone marrow, where low levels of antibodies are secreted throughout the life of the plasma cell. Both IgM and IgG alloantibodies can be detected in the serum as well as in the graft of animals and humans undergoing allograft rejection. Preformed anti-HLA Class I antibodies, and occasionally anti-endothelial antibodies, play an important role in hyperacute rejection and accelerated vascular rejection seen in previously sensitized transplant recipients [9].

Events culminating in hyperacute rejection include binding of complement components, which themselves can cause direct damage through the membrane attack complex (MAC), and indirectly through chemokine properties of complement breakdown products, C3a and C5a, as well as deposition of platelets and fibrin, infiltration by granulocytes and monocytes, and fibrinoid necrosis of the vessel wall. This form of rejection manifests within minutes to hours after transplant, leading to graft failure as well as systemic manifestations such as disseminated intravascular coagulopathy. Fortunately, the incidence of hyperacute rejection has decreased significantly by employing routine HLA cross-matching screening, as well as avoiding ABO incompatilbility, prior to transplantation [10].

1.2.3.2 Acute Rejection

HLA differences activate a variety of events that result in acute cellular rejection and also set the stage for the development of chronic rejection. Recent advances in molecular and cellular immunology have further unraveled interactions between APC and T and B cells. These include elucidation of pathways involved in T-cell activation and apoptosis; identification of novel regulatory cells, including T-regulatory cells, B-regulatory cells, and suppressive APCs; as well as greater appreciation of the complex interactions between innate and adaptive immunity. Furthermore, elucidation of triggers of B-cell activation and antibody synthesis have allowed for the development of B-cell-specific immunosuppression.

Since T cells serve as the central hub in the cascade of alloimmunity, a brief overview of the current understanding of T-cell activation and proliferation is warranted. Optimal activation of naïve T cells requires coordinated signal transduction through three pathways: (1) nuclear factor-κB (NF-κB) pathway, (2) mitogen-activated protein (MAP) kinase-induced activator protein-1 (AP-1) activation, and (3) calcium-dependent calcineurin dephosphorylation of nuclear factor of activated T cells (NFAT) [11, 13]. Antigen-specific T cells interact with APC through the T-cell receptor (TCR)/MHC Class II molecule (signal 1) and CD28 costimulatory molecule/B7 (CD80 and CD86) molecules (signal 2) within the contact area, also

known as the "immunological synapse." Subsequently, phosphorylation of the immunoreceptor tyrosine-based activation motifs (ITAMs) on the CD3 cytoplasmic tail results in downstream activation of protein kinase C (PKC) and MAP kinase with resultant activation of transcription factors, in particular NF-κB and AP-1 [12]. In addition, PKC appears to synergize with the serine/threonine phosphatase, calcineurin, to dephosphorylate NFAT to bind to a nuclear translocating protein. These cytoplasmic factors translocate to the nucleus, where they bind to their respective response elements, leading to gene transcription and synthesis of a variety of proteins, including interleukin-2 (IL-2), the α-chain of the IL-2 receptor (CD25), the CD40 ligand (CD154), interferon gamma, tumor necrosis factor α and β (TNF-α and TNF-β), and stem cell growth factors (e.g., granulocyte colony stimulatory factor) [12]. Secreted factors, in particular IL-2, bind in an autocrine or paracrine manner to their corresponding receptors on the T-cell surface to deliver signal 3 by activation of Janus kinase (JAK), in particular the JAK-3 isoform. This in turn leads to activation of other key downstream regulatory proteins, including FRAP, also known as mTOR ("mammalian target of rapamycin"). mTOR plays a key role in the signal transduction pathways downstream to many growth factor receptors (including the IL-2 receptor). This results in DNA synthesis and initiation of T-cell clonal proliferation as well as generation of effector T cells [14]. Other cytokines, such as IL-4, induce B-cell maturation and antibody synthesis, while other cytokines have pleomorphic effects, such as smooth muscle proliferation, and induce fibroblast proliferation, all hallmarks of chronic rejection [15–18]. Fortunately, the incidence of acute rejection is more frequent in the initial 6 weeks after engraftment and declines in incidence and severity after this period [19]. Nevertheless, for memory T cells, the need for costimulation is eliminated, and TCR-CD3/antigen-MHC engagement is all that is required for subsequent T-cell proliferation.

Once the antigen is consumed or removed, the process downregulates by virtue of several events. APC presents a negative costimulatory signal, CTLA4, which opposes the positive action of CD28. In addition, T-regulatory cells (Tregs), which bear CD25 and CTLA4, are generated. These cells inhibit T-cell proliferation in both animals and humans. Both CTLA4 and Tregs appear to induce activated T-cell apoptosis, also known as programmed cell death, a process of DNA fragmentation [20, 21].

1.2.3.3 Chronic Rejection

Progressive decline in allograft function, months or years after transplantation, is manifested by gradual vascular obliteration (a hallmark in all types of allografts), eventually leading to fibrosis and allograft dysfunction [22]. In addition, each organ system may have specific manifestations of chronic allograft rejection, such as "vanishing bile duct syndrome" in the livers, accelerated diffuse coronary artery allograft vasculopathy in hearts, bronchiolitis obliterans in the lungs, recurrent diabetes mellitus in the pancreas, and chronic allograft nephropathy in the kidneys. Immunological factors, such as episodes of acute rejections, degree of histoincompatibility, and level of pre-sensitization, as well as other non-immunological factors, such as: ischemia reperfusion injury, hyperlipidemia, immunosuppressive drug toxicity, and infection-related allograft inflammation, contribute to chronic allograft

dysfunction. Occurrences of episodes of acute rejection predispose to the development of chronic rejection in several studies [23]. Alternatively, indirect allorecognition may result in chronic rejection. Experimental evidence suggests that infiltration of host APC into the graft, which is depleted of APC, makes it susceptible to chronic rejection [24].

1.3 Immunosuppression

1.3.1 Introduction

Prior to the advent of immunosuppression, transplant recipients received total body irradiation to suppress the immune response, and all ended with poor outcomes. The first breakthrough in immunosuppression occurred when Dameshek and Schwartz reported the development of 6-mercaptopurine (6-MP) [25]. Calne reported on the successful use of 6-MP for renal transplants in dogs [26]. This was followed by the report that azathioprine (AZA), a derivative of 6-MP, was as effective and less toxic, facilitating its widespread use in 1962. Starzl combined AZA and steroids, which became the standard regimen for renal transplantation prior to the advent of T-cell-specific immunosuppression. The ability to minimize hyperacute rejection with the introduction of crossmatching resulted in improved early survival after kidney transplantation. Subsequently, the application of the more targeted immunosuppressive agents, cyclosporine and then tacrolimus, further reduced the risk of immunologic loss after transplantation and greatly contributed to making transplantation routinely successful.

Optimal immunosuppression as it relates to transplantation is defined as the level of drug therapy that achieves graft acceptance with the least suppression of systemic immunity. In so doing, the amount of systemic toxicity, namely, infection and malignancy, in addition to drug-specific side effects, is minimized, although not entirely eliminated [27]. Therapeutic drug monitoring and titration of immunosuppression is limited to only a few immunosuppressive agents, and, in practice, over- or under-immunosuppression almost invariably becomes apparent only in retrospect.

The use of immunosuppressive agents in transplantation can be categorized into three settings: (1) initial induction therapy with potent suppression of the immune response, (2) maintenance therapy to minimize the risk of acute and chronic rejection while maximizing immune competency and minimizing toxicity, and (3) reversal of acute and/or stabilization of chronic rejection episodes. A fine balance is required between the potency and the toxicity of these agents, in some cases requiring therapeutic drug monitoring. As mentioned earlier, occurrence of acute rejection episode(s) may predispose to chronic rejection, even though the acute rejection episode is treated adequately. Although this underscores the traditional dogma "prevention is better than cure," it is now appreciated that in order to achieve the Holy Grail of transplantation, namely, tolerance, some immune activation is necessary. Whether newer immunosuppressive agents are able to allow selective activation of pro-tolerant regulatory pathways remains to be seen in the clinical setting.

In order to better understand the use of immunosuppressive agents, it is helpful to categorize their mechanisms of action, such as antimetabolite, depleting, anti-inflammatory, inhibition of cytokine synthesis, and inhibition of growth factor proliferation. Most immunosuppressive regimens utilize combinations of these agents to obtain additive or synergistic effects of the various classes of agents while minimizing their toxicity. As the T-cell response is the hub of activation of other downstream effector mechanisms of alloimmunity, it is not surprising that most approved immunosuppressive agents are targeted to directly or indirectly control the T-cell response. Nevertheless, several drugs have been utilized in transplantation targeted to these downstream effector pathways, such as the alloantibody response and cytokine-driven myofibroblast proliferation.

1.3.1.1 Antimetabolites

Azathioprine (AZA)

AZA is a purine nucleoside analogue and an inactive prodrug. It is well absorbed after oral administration and is metabolized in the liver to the active drug 6-MP, which in turn is converted to active metabolite thioinosinic acid (TIMP). 6-MP is catabolized via the thiopurine methyltransferase and the xanthine oxidase pathways, with the final metabolites excreted in the urine. Hence, the main immunosuppressive activity of AZA depends on the metabolism to thioguanine nucleotides [28]. Thioguanine nucleotides are incorporated into and damage DNA and RNA, causing inhibition of transcription and arrest of cell proliferation [29]. TIMP inhibits the enzymes adenylosuccinate synthetase, adenylosuccinate lyase, and inosine monophosphate dehydrogenase, thus interfering with guanylic and adenylic acid synthesis from inosinic acid. TIMP is converted to thioguanylic acid, which is incorporated into DNA, thus interfering with DNA synthesis. AZA suppresses proliferation of activated B and T lymphocytes and also decreases the number of circulating monocytes by arresting bone marrow promyelocyte cell cycle.

AZA use has fallen with the availability of mycophenolic acid derivatives (see "mycophenolic acid") and is now largely used in treatment of autoimmune diseases. The major nonimmune toxic side effect of AZA is dose-limiting bone marrow suppression (BMS), leading to pancytopenia. Hence, monitoring of blood counts is used to guide dosing. The hematological side effects are generally reversible, when AZA dosage is reduced or when it is temporarily discontinued. As with other antiproliferative immunosuppressants, nausea, vomiting, and reversible hair loss may occur with AZA. AZA may also cause reversible cholestasis and infrequently results in severe veno-occlusive liver disease [30] and interstitial pneumonitis. It can be also associated with pancreatitis, assumed to be secondary to a hypersensitivity reaction [31]. It appears to be safer to use in pregnancy than other antiproliferative agents, as fetal cells lack the enzyme necessary to produce potentially toxic thioguanine nucleotides.

The interaction between AZA and allopurinol deserves special attention. Allopurinol inhibits xanthine oxidase, which is an important route of drug elimination for AZA – inhibiting the breakdown of AZA and its metabolites. This results in enhanced toxicity of AZA, thus necessitating dramatic dose reduction. Severe and

prolonged neutropenia with sepsis has been reported in patients treated concomitantly with both drugs [32]. A safer alternative for patients requiring allopurinol is to substitute AZA with mycophenolate derivatives.

Mycophenolic Acid

Mycophenolate mofetil (MMF) is an immunosuppressant introduced for use in transplantation [33–39]. MMF is a prodrug form of mycophenolic acid (MPA) and was developed as a replacement for AZA and currently is a cornerstone in a number of maintenance regimens. After absorption, it is rapidly converted to its active metabolite MPA via hydrolysis. MPA is a reversible noncompetitive inhibitor of inosine monophosphate dehydrogenase (IMPDH), which is a key enzyme in the de novo synthesis of guanosine monophosphate (purine synthesis pathway). This inhibition of IMPDH causes a deficiency of guanosine and deoxyguanosine nucleotides (preventing DNA and RNA synthesis) and a relative excess of adenosine nucleotides (inhibits 5-phosphoribosyl-1-pyrophosphate synthase, which further halts the purine synthesis). Hence, MPA selectively inhibits lymphocyte proliferation as lymphocytes are relatively dependent on the de novo purine synthesis pathway. In vitro, MPA suppresses antibody formation, inhibits cytotoxic T-cell production, and reduces the expression of certain adhesion molecules.

MPA is 90 % bound to plasma proteins. The main pathway of elimination is by hepatic glucuronidation and excretion in both the stool and urine. Of note is that the biliary excreted form of MPA glucuronide metabolites can undergo bacterial breakdown and reabsorption, also known as the enterohepatic circulation where inactive MPA is converted back to active MPA by glucuronidases from gut flora.

The results from various trials related to renal transplant, including multicenter double-blinded placebo-controlled trials, have shown that MMF-treated patients have a significant decrease in the incidence of acute rejection when compared to patients treated with placebo or AZA without an increase in the adverse events [35].

MMF is usually well tolerated. The major side effects are related to gastrointestinal symptoms such as nausea, vomiting, and diarrhea, which subside with a decrease in the dose of MMF. The gastrointestinal symptoms are believed to be secondary to the dependency of the gastrointestinal tract epithelial cells on IMPDH. MMF does not cause nephrotoxicity, hepatotoxicity, or significant bone marrow suppression, but patients treated with MMF may be more likely to develop invasive CMV disease [38]. In addition, MPA/MMF use during pregnancy has been associated with microtia and facial dysmorphic features in the offspring [39] and recommendations include discontinuing MMF/MPA at least 6 weeks prior to becoming pregnant.

1.3.1.2 Anti-inflammatory

Corticosteroids

Synthetic glucocorticoids have been used for all phases of transplant immunosuppression including induction and maintenance immunosuppression, as well as for treatment of acute rejection episodes. Prednisone, prednisolone, methylprednisolone,

and hydrocortisone are the main compounds used in transplantation. Oral absorption of glucocorticoids is otherwise very high, and they are 90 % bound to plasma proteins. Hepatic p450 enzymes metabolize the glucocorticoids, but rarely do inducers or inhibitors of the p450 enzymes require a dose adjustment of glucocorticoids.

Corticosteroids possess both immunosuppressive and anti-inflammatory properties [40]. The pharmacologic effects include suppression of macrophage function, prevention on T lymphocyte proliferation, inhibition of cytokine production (in particular IL-1), reduction in adhesion molecule expression, induction of lymphocyte apoptosis, alteration of leukocyte trafficking, inhibition of leukocyte transmigration through blood vessels, and reduction of MHC expression. Other effects also include suppression of prostaglandin synthesis, decreasing capillary permeability, inhibiting histamine and bradykinin release, as well as reducing the absolute number of neutrophils and eosinophils. Corticosteroids bind to the intracytoplasmic receptors within target cells to form an active corticosteroid receptor complex (CRC), which binds to the DNA in the nucleus at the corticosteroid response element (CRE) of the promoters of target genes. The CRC and the CRE interaction results in induction or suppression of the transcription of the target genes. It activates the gene that inhibits the activity of NF-kB (an important transcriptional activator for many proinflammatory cytokines) [41].

The administration of corticosteroids is typically recommended as a single morning dose to resemble the standard physiologic rhythm of the pituitary-adrenal axis. High-dose intravenous methylprednisolone is the standard therapy for acute rejection (250–500 mg/day for 3 days) and effectively reverses 85–90 % of acute rejection episodes. Oral prednisone in equivalent doses can also be used with comparable results.

Frequent side effects of corticosteroids include hypertension, hyperlipidemia, diabetes mellitus, peptic ulceration, poor wound healing (impaired fibroblast growth and collagen synthesis), proximal muscle weakness, osteoporosis, and growth retardation in children (suppression of pituitary-adrenal axis). Less common side effects include pancreatitis, psychosis, posterior subcapsular cataract, and avascular necrosis of the femoral head. The classic "Cushingoid" features are secondary to soft tissue and dermatologic changes (fat redistribution, skin atrophy, striae, and acne). Acute adrenal insufficiency can develop, even up to 12 months after cessation of steroids, when the patient is stressed. Hence, corticosteroids used in transplantation carry considerable potential for morbidity [40, 42]. Protocols that minimize or avoid the use of glucocorticoids have been advocated in a variety of solid organ transplant trials, but given the higher rates of rejection seen, this practice often requires the use of other adjuvants or induction immunosuppression.

1.3.1.3 Inhibition of Cytokine Synthesis

Cyclosporine (CsA)

CsA is a natural lipid-soluble cyclic 11-amino-acid peptide isolated from the fungus *Tolypocladium inflatum*. It is insoluble in water and has a variable oral bioavailability of approximately 30 % [43]. Complex preparations are essential to ensure absorption in the oral formulation due to its insolubility. The original oral formulation

(Sandimmune™) was bile dependent, and its incomplete emulsification yielded marked interindividual variations in bioavailability. The microemulsion formulation has more predictable pharmacokinetics, i.e., better absorbed, bile independent, and provides more consistent blood levels. The relative bioavailability is increased between 74 and 139 % [44], and the total area under the concentration-time curve (AUC) is increased by 30 % [45], when compared to the original conventional preparation. Once absorbed, it is extensively bound to red blood cells and plasma proteins, with only 5 % of the drug free in plasma. It is eliminated mainly via hepatic metabolism, and the drug metabolism is via cytochrome P450 IIIA enzymes [46].

CsA functions to prevent antigen-specific T-cell activation, and this immunosuppressive effect is well established [28, 47]. CsA acts by binding to cyclophilin, which is a cytoplasmic protein that belongs to the immunophilin family. The CsA-cyclophilin complex inhibits calcineurin (CN), which is a calcium-dependent serine phosphatase, preventing the activation of several CN-dependent transcription factors, including NFAT (nuclear factor of activated T cells). This results in the inhibition of the expression of T-cell cytokines such as IL-2, IL-3, IL-4, IFN-γ, TNF-α, and GM-CSF, exerting an effective immunosuppressive effect. On the other hand, the expression of TGFβ is promoted in the presence of CsA, which inhibits T-cell activation, but may promote renal fibrosis, a result of long-term CsA therapy [48].

Nephrotoxicity is the most important nonimmune side effect of CsA and is mediated by afferent arteriolar vasoconstriction, believed to be caused by CN inhibition [49–51]. Characteristic biopsy findings in advanced chronic nephrotoxicity are "striped" interstitial fibrosis and arteriolar hyalinization. CsA levels are usually high in acute nephrotoxicity, but not necessarily so in chronic nephrotoxicity. CsA is diabetogenic, although simultaneous use of corticosteroids muddles the cause of diabetes. Other side effects include neurotoxicity, hypertension [51], hyperuricemia, hyperkalemia, hyperlipidemia, hypertrichosis, gingival hypertrophy, coarsening of facial features [52], and transient hepatotoxicity. Although CsA trough monitoring is not a good predictor of its immunosuppressive effect, it is a common practice to measure blood levels and make dose adjustments because of its narrow therapeutic window.

Tacrolimus (FK506)

Perhaps the most studied and most commonly utilized immunosuppressive drug is tacrolimus (FK). FK is a macrolide antibiotic isolated from the bacterium *Streptomyces tsukubaenis*. FK is superior to CsA in terms of immunosuppressive efficacy, as validated by several clinical trials [53–64], and the relative resistance of FK to p-glycoprotein countertransport, which decreases the intracellular drug levels, may be contributing to its enhanced efficacy. Patients treated with FK have less frequent and less severe rejection episodes compared to CsA-based immunosuppressive protocols.

FK binds to an immunophilin, FK-binding protein (FKBP), in the cell cytoplasm. FK-FKBP complex inhibits CN activity, similar to the mechanism of CsA. FK has additional immunosuppressive effects in vitro, independent of NFAT inhibition [28, 47]. FK is much more potent than CsA on a mg-to-mg comparison. FK is also

variably absorbed, and thus therapeutic drug monitoring is essential – to achieve efficacy while minimizing the risk of toxicity [66–68]. FK has a half-life of 12 h; hence, it is administered 12 h apart (two daily doses) – although rarely indicated, FK can also be given intravenously at 30 % of the oral dose. Goal levels vary by organ type, duration posttransplant, and other factors. Recently, a once daily formulation has been investigated with promising results, particularly related to compliance and quality of life measures [69].

The degree of nephrotoxicity caused by FK appears to be equivalent to CsA [70–72]. FK is associated with neurotoxicity [72] and is also diabetogenic [62, 63] but is not associated with hypertension, gingival hypertrophy, hypertrichosis, or hypercholesterolemia. Gastrointestinal side effects such as diarrhea and anorexia are comparable to those seen with other macrolide antibiotics, like erythromycin.

1.3.1.4 Depleting Antibodies

OKT3

OKT3 is a murine monoclonal antibody directed against 20,000 Da CD3 complex of molecules on the surface of thymocytes or mature human T cells [73]. As CD3 associates with the T-cell receptor (TCR), essential for antigen recognition and function [74–76], the immunosuppressive effects of OKT3 are in part mediated by modulation or removal of CD3/TCR complex from the T-cell surface via shedding or endocytosis, thus rendering the T cells dysfunctional and immunologically incompetent [77–81].

OKT3 was the first monoclonal antibody to be used in mainstream clinical medicine. In transplantation, OKT3 was shown to be very effective for the treatment of severe acute rejection and was also widely used for induction immunosuppression. Concerns of early lymphoproliferative disease in OKT3-treated patients limited its prophylactic use, and as other antilymphocyte antibody preparations became available, OKT3 was subsequently phased out of production. Nevertheless, many of the lessons learned with the use of OKT3 apply to these newer agents and are worth discussing.

The most common side effect of OKT3 is the cytokine-release syndrome (CRS), which typically began 45–60 min after the initial dose and lasted up to several hours. It resulted in fever, chills, myalgia, weakness, and gastrointestinal (nausea, vomiting, diarrhea) and pulmonary (bronchial spasms) symptoms. This symptom complex was attributable to a variety of mediators, including cytokines, released from T cells activated by the binding of OKT3 to the CD3-TCR complex [84]. Premedication with steroids, antihistamine, and antipyretics, especially indomethacin, generally reduced the severity of the first dose effect. Significant suppression of the cell-mediated immunity predisposes to opportunistic infections and malignancies. Neurological adverse effects include headache, convulsion, and aseptic meningitis. Lastly, the use of OKT3 was associated with a high incidence of the development of host antibodies to the murine immunoglobulin, both to the idiotype and structural epitopes [82, 83]; thus, it is generally advisable to measure the human anti-mouse antibody (HAMA) titers in patients prior to retreatment with a second course of any murine monoclonal antibody.

Antithymocyte Globulin (ALG)

Antithymocyte globulin (ATG) is a member of a class of agents of polyclonal antibodies directed against immunocytes. While ATG's mechanism of action is incompletely understood, ATG has been shown to cause T-cell depletion by inducing apoptosis as well as complement- and antibody-mediated pathways [84]. The current FDA-approved ATG formulation (Thymoglobulin) is a polyclonal rabbit anti-human thymocyte globulin (RATG) obtained by immunization of rabbits with human thymocytes. It was approved by the FDA in 1999 for the treatment of acute renal graft rejection in conjunction with concomitant immunosuppression. ATG contains cytotoxic antibodies directed against a variety of antigens expressed on human T lymphocytes. ATG includes antibodies against T-cell markers such as CD2, CD3, CD4, CD8, CD11a, CD18, CD25, CD44, CD45, HLA-DR, HLA Class I heavy chains, and ß2-microglobulin.

Currently ATG remains widely used in a variety of settings including induction regiment and patients with concern for renal insufficiency, (in order to minimize early exposure to calcineurin inhibitors), and in cases of acute rejection [85], ATG is associated with a variety of side effects in both the acute and delayed settings. In the acute setting ATG can be associated with a cytokine-release syndrome characterized by fevers, chills, shortness of breath, tachycardia, hypotension, and, in the extreme setting, cardiovascular collapse. Additionally, cross-reactivity of the serum can result in pancytopenia and thrombosis [86].

1.3.1.5 Anti-growth Factor-Induced Proliferation

Anti-IL-2 Receptor Alpha-Chain Antibody: Basiliximab

Basiliximab (Simulect, Novartis Pharma) is a chimeric monoclonal antibody developed to target the alpha chain of the IL-2 receptor (CD25). As mentioned earlier, IL-2 plays an important role in expansion of T cells as well as T-cell cytokine production. Basiliximab has been used as induction therapy in solid organ transplant as well as in the treatment of episodes of acute rejection. One study comparing basiliximab to ATG induction therapy in renal transplant recipients at high risk of delayed graft function or acute cellular rejection observed no difference in overall or graft survival at 1 year, while there were significantly fewer episodes of acute rejection [87]. These findings were found to be similar on 5-year follow-up [88]. In liver transplant recipients, basiliximab has been shown to be efficacious as well as to decrease rates of rejection, to improve 2-year graft, and to improve overall survival compared to regiments without induction therapy [89]. In liver recipients, basiliximab is most often used in patients with renal dysfunction at time of transplant in order to delay CNI initiation [90]. In the pediatric transplant population, basiliximab remains the most often utilized induction agent. The drug is typically dosed at 20 mg dose for adults and pediatric patients over 35 kg and at 10 mg/dose for those <35 kg [91]. A mechanistically similar humanized monoclonal antibody against CD-25, daclizumab (Roche), has been used and studied with similar effects including decreased incidence of acute rejection and as an induction agent to allow delayed CNI initiation for patients with some renal insufficiency. It has been removed for marketing reasons and is no longer available in the USA or Europe [92].

1.3.1.6 Mammalian Target of Rapamycin (mTOR) Inhibitors

Rapamycin (Sirolimus, RAPA)

Rapamycin is a macrolide antibiotic structurally related to tacrolimus. It binds to FKBP-12 but does not inhibit cytokine gene transcription in T cells. It blocks signals transduced from the IL-2 receptor and other growth factors to the nucleus by acting on phosphatidylinositol kinases, also known as "mammalian target of rapamycin" (mTOR). It also inactivates p70S6 kinase resulting in selective inhibition of the synthesis of new ribosomal proteins and prolonging cell cycle progression from G1 to G2 [93]. Thus, the mechanism of action differs significantly from either Tac or CsA in that RAPA inhibits both B- and T-cell responses to alloantigen [94].

RAPA has a poor bioavailability after oral administration and the dosing frequency is once daily. Therapeutic monitoring of sirolimus should be based on whole blood concentrations because of the high sequestration of sirolimus by erythrocytes [95]. The adverse effect profile of sirolimus is unique compared to other immunosuppressants. Unlike cyclosporine and tacrolimus, nephrotoxicity and neurotoxicity are rarely seen with sirolimus. The side effects with rapamycin include GI disturbances, diabetes mellitus, myocardial necrosis, and testicular atrophy. Because RAPA acts to suppress growth factor-driven proliferation, dose-dependent myelosuppression can be seen following initiation of sirolimus therapy in particular at higher drug concentrations [96, 97]. In addition, fibroblast proliferation is suppressed, leading to a higher rate of wound complications, such as lymphocele formation, wound disruption, and hernia formation [98, 99]. Hyperlipidemia is commonly seen in patients receiving sirolimus, manifesting as hypercholesterolemia and hypertriglyceridemia. This effect has been reported in virtually all clinical trials.

1.3.1.7 SDZ-Rapamycin (Everolimus, EVR)

Everolimus (EVR) is an analogue of rapamycin, acting in a similar fashion to sirolimus (Fig. 1.1). It differs from sirolimus in several pharmacologic aspects (Table 1.1), which alters dosing frequency (usually twice-a-day dosing) and use of concomitant dosing with other immunosuppressive medications.

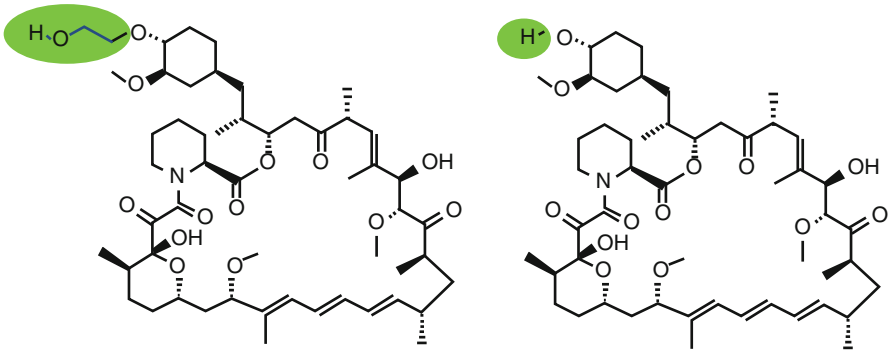

Fig. 1.1 Structure of mTOR inhibitors, everolimus (*left*), and sirolimus (*right*). Everolimus differs from sirolimus due to the addition of a 2-hydroxyethyl group at C_{40}

Table 1.1 mTOR inhibitors – key clinical differences

	Sirolimus	Everolimus
Oral bioavailability	14 %	20 %
Time to T_{max}	1–2 h	1–2 h
Half-life	62 h	28 h
Loading dose	6.0 mg	No
Time to steady state	5–7 days	4 days
Plasma protein binding	92 %	74 %
Dosing interval	Once daily	Twice daily
Target trough levels	4–12 ng/mL	3–8 ng/mL
Concomitant dosing with CsA	4 h post-CsA dose	Yes

During the initial trials in de novo renal transplant patients, EVR was utilized with full-dose CsA but was quickly adjusted to utilize low-dose CsA due to increased nephrotoxicity. In the ZEUS trial, an open-label, randomized control study evaluating the use of EVR with CNI withdrawal for renal transplant recipients, patients received usual dosing of mycophenolate sodium, corticosteroids, and cyclosporine for the first 4.5 months at which point the study patients were randomized to either continued cyclosporine-based therapy or conversion to EVR with withdrawal of CsA. The EVR group was shown to have a significantly improved eGFR compared to the cyclosporine group (71.8 vs 61.9 mL/min per 1.73 m^2). Twelve-month BPAR was similar between the groups; however, there was an increased rate of BPAR during the period of CNI withdrawal compared to continued CNI group. Graft loss and death were similar among the groups at 12 months post-kidney transplant [100].

A phase 3 multicenter, randomized, controlled study to evaluate the efficacy and safety of concentration-controlled EVR to minimize and/or eliminate tacrolimus in de novo LTX recipients recently completed enrollment with 2-year follow-up. A total of 719 adult LTX recipients were initially treated with tacrolimus and steroids with/without MMF during a 30-day immediate post-LTX period. At that point, screened patients were then randomized into one of three treatment arms (everolimus with tacrolimus elimination, low-dose everolimus with low-dose tacrolimus, or standard tacrolimus). The primary objective was modified to a standard efficacy failure (biopsy-proven acute rejection, graft loss, death) with a key secondary endpoint to demonstrate superior renal function in the everolimus treatment groups, compared to tacrolimus control at month 24. In this study, there was a significantly increased incidence of rejection in the group of patients where tacrolimus was eliminated. The incidence occurred during the weaning of tacrolimus. Although patient survival and graft survival were not affected, there was an early increase in BPAR in groups that had tacrolimus elimination. At the end of 24 months, there was no difference in the primary endpoint of efficacy failure; however, the incidence of biopsy-proven acute rejection was statistically lower in the low-dose everolimus/tacrolimus group than the control group. Of great interest was the finding that the eGFR was significantly higher in the low-dose everolimus/tacrolimus group

compared to the control group [101]. This study has been extended to evaluate 36- and 48-month outcomes with no further increased incidence of rejection with continued improvement in eGFR of the low-dose everolimus/tacrolimus group in early reports [102].

1.3.1.8 New Immunosuppressive Agents

Novel therapeutic strategies are currently being employed either clinically or are undergoing clinical testing in solid organ transplantation and may have promise as new or adjunctive immunosuppressive agents. They can be categorized into:

1. Inhibitors of signal 1: TCR blockade
2. Inhibitors of signal 2: costimulatory blockade
3. Inhibitors of signal 3: inhibition of growth factor-driven proliferation

1.3.1.9 Signal 1 Inhibition

TOL101

TOL101 (T10B9, MEDI-500) is a murine IgM k chain mAb directed against the alpha and beta subunits of the TCR and appears to lead to internalization of the TCR rather than T-cell depletion. The predecessor antibodies for TOL101, T10B9, and MEDI-500 have been administered to approximately 135 patients across 13 studies from 1986 to 2000 – over 100 of these patients were recipients of solid organ transplants. The largest of these studies was a 76-patient phase 2 trial investigating T10B9 vs. OKT3 (at that time, considered standard of care) for the treatment of acute renal transplant rejection. Graft survival and subject survival were high (>80 %) over 4 years and similar between the two treatment groups. The incidence and severity of adverse events (including fever, respiratory symptoms, gastrointestinal complaints, and neurological symptoms) were substantially higher in the OKT3 group than in the T10B9 recipients [103]. TOL101 is currently in a phase 1/2 study as part of an immunosuppressive regimen that includes tacrolimus, MMF, and steroids in patients undergoing primary kidney transplantation. Because of the large size of this molecule, the pharmacokinetic profile of this agent may be more favorable (due to longer intravascular retention) in LTX patients, where pharmacokinetics demonstrated higher clearance of IgG preparations.

Sotrastaurin

Sotrastaurin (AEB071) is a novel immunosuppressant that blocks early T-cell activation via inhibition of PKC, integrating in particular signaling pathways downstream of the T-cell receptor (TCR) and the CD28 co-receptor. Sotrastaurin has been shown to specifically inhibit early T-cell activation through signals 1 and 2 but not T-cell proliferation (signal 3) by selectively blocking the calcineurin-independent pathway signaling through NF-kB resulting in inhibition of cytokine gene transcription. AEB071 is being developed for the prevention of acute rejection in solid organ allotransplantation in combination with or without a calcineurin inhibitor (CNI). In

contrast to CNIs, AEB071 potently and selectively blocks a calcineurin-independent pathway pointing toward a clear differentiation in mode of action and possibly the side effect profile between AEB071 and CNIs.

Thus far, sotrastaurin has been used in two phase 2 de novo renal transplant trials. In one study, recipients were randomized to sotrastaurin (200 mg b.i.d.) + standard-exposure tacrolimus (SET) or reduced-exposure tacrolimus (RET) (SET: $n=76$; RET: $n=66$) or control (SET + MPA, 720 mg b.i.d.; $n=74$) [104]. In both sotrastaurin groups, patients were converted from tacrolimus to MPA after month 3, achieving CNI-free immunosuppression. The primary endpoint was composite efficacy failure (treated biopsy-proven acute rejection, graft loss, death, or loss to follow-up), while the key secondary endpoint was GFR. Composite efficacy failure rates were 4.1, 5.4, and 1.5 % at month 3 (pre-conversion) and 7.8, 44.8, and 34.1 % at study end in the control, sotrastaurin + SET, and sotrastaurin + RET groups, respectively. In addition, the median GFR at month 6 was 57.0, 53.0, and 60.0 mL/min/1.73 m^2, respectively. Based on the primary endpoint, the Data Safety Monitoring Board (DSMB) recommended premature study discontinuation. Although the initial sotrastaurin + tacrolimus regimen was efficacious and well tolerated and the postconversion sotrastaurin + MPA regimen showed inadequate efficacy, longer-term evaluation of sotrastaurin + tacrolimus appears warranted.

In another study, de novo renal transplant recipients with immediate graft function were randomized 1:2 to tacrolimus (control, $n=44$) or sotrastaurin (300 mg b.i.d.; $n=81$) [5]. All patients received anti-IL2-RA, MPA, and steroids. The endpoints were similar to that noted in the previous trial. In this trial, the composite efficacy failure at month 3 was higher for the sotrastaurin versus control regimen (25.7 % vs. 4.5 %, $p=0.001$) with rejection rates higher in the sotrastaurin group compared to control, 23.6 % vs. 4.5 %, respectively ($p=0.003$), which led to early study termination by the DSMB. Of great interest was the finding that the median estimated GFR was higher for sotrastaurin versus control at month 3: 59.0 vs. 49.5 mL/min/1.73 m^2 ($p=0.006$) [105]. Further follow-up studies have been recently completed showing reasonable efficacy but decreased tolerability compared to current standard regiments [106].

1.3.1.10 Signal 2 Inhibition

Abatacept (CTLA4-Ig)/Belatacept (LEA29Y)

Abatacept is a chimeric fusion protein that consists of the extracellular domain of CTLA-4, and the Fc domain of IgG blocks the B7 (CD80, CD86)/CD28 pathway. This agent is approved for use in moderate to severe psoriasis. Belatacept is a molecular mutation of abatacept, differing from abatacept in two amino acid positions in the binding domain to B7, associated with a higher binding avidity and slower dissociation rate, with resultant inhibition of T-cell activation greater than that of abatacept. With both molecules, blockade of the B7/CD28 interaction leads to inhibition of T-cell proliferation. Belatacept was investigated in a phase 2 de novo kidney transplant trial with a CsA regimen as control. This trial consisted of belatacept injections every 2 weeks for 1 year. There was an improvement in the GFR in

the belatacept-treated group compared to the CsA group, but there was no difference in biopsy-proven acute rejection [107]. In follow-up pivotal phase 3 trials, belatacept demonstrated 1-year subject and graft survival that was comparable to CsA, with improved renal function and less metabolic complications such as incidence of new-onset diabetes mellitus, blood pressure, and abnormal lipid profile [108]. An increased risk of posttransplant lymphoproliferative disorder (PTLD), particularly among Epstein-Barr virus-negative recipients, was a notable adverse event. However, belatacept was associated with an increased frequency of early acute rejection compared with CsA. With longer-term follow-up, the impact of these rejections appeared to be limited. Extended follow-up over 3 years demonstrated evidence of ongoing efficacy, which did not differ between the two belatacept dose regimens (LI and MI) evaluated, and in particular, GFR was better preserved in both belatacept groups, even in those that experienced an acute rejection, compared to CsA-treated recipients. In addition, the incidence of chronic allograft nephropathy was also significantly lower in the belatacept-treated patients [109, 110]. Based on this data, belatacept was recently approved by the FDA for kidney transplantation. The additional long-term benefits that accrue to patients on belatacept relating to improvements in metabolic parameters have been fully assessed.

Belatacept was next investigated in a phase 2b multicenter prospective partially blind clinical trial in LTX [111]. Five treatment groups were utilized: Group 1, anti-IL2RA + belatacept more intensive (MI) + MMF; Group 2, belatacept (MI) + MMF; Group 3, belatacept less intensive (LI) + MMF; Group 4, tacrolimus + MMF; and Group 5, tacrolimus. The primary objective was to evaluate the effects of belatacept relative to TAC on the triple composite endpoint of the incidence of acute rejection (AR), death, and graft loss by 6 months after receiving a deceased donor transplant. An imbalance in deaths in the belatacept treatment arms relative to the tacrolimus + MMF arm was noted. The frequencies of death were noted as 12, 21, and 22 % in the anti-IL2RA + belatacept MI + MMF, belatacept MI + MMF, and belatacept LI + MMF arms, respectively, in comparison to 6 % in the TAC + MMF arm and 14 % in the TAC arm. Of note was the marked difference in GFR in the belatacept groups compared to the control groups. There were two reports (one fatal) of PTLD and one report of fatal progressive multifocal leukoencephalopathy (PML). In addition there was an increase in viral and fungal infections in the combined belatacept groups versus the tacrolimus groups, potentially due to the degree of immunosuppression.

Future trials with belatacept may possibly include a short period of CNI exposure in the perioperative period, and these considerations are ongoing at this time.

Efalizumab

Efalizumab is a humanized IgG1 mAb directed against the leukocyte function-associated antigen-1 (LFA-1, CD11a). CD11a plays an important role in adhesion of leukocytes to endothelial cells and also serves as a costimulatory molecule. Approved for treatment of moderate to severe psoriasis, a pilot study was performed in 38 primary kidney transplant recipients [11]. Patients were randomized to receive efalizumab 0.5 or 2 mg/kg weekly subcutaneously for 12 weeks. Patients were maintained on full-dose CsA, MMF, and steroids ($n = 10$ 0.5 mg/kg efalizumab,

$n=10$ 2.0 mg/kg efalizumab) or half-dose CsA, sirolimus, and prednisone ($n=9$ 0.5 mg/kg efalizumab, $n=9$ 2.0 mg/kg efalizumab). At 6 months following transplant, patient survival was 97 % and graft survival was 95 %. Clinical biopsy-proven acute rejection in the first 6 months after transplantation was confirmed in one of each of the immunosuppressive combination (e.g., 4/38, 11 %). Three patients (8 %) developed PTLD, all in the highest dose efalizumab with full-dose CsA [112]. Although this drug appeared promising, subsequent reports of the development of PML in patients treated for extended periods with efalizumab for psoriasis resulted in withdrawal of this agent from the market [113]. Nevertheless, interference of this pathway is seemingly a novel approach for future trials.

Alefacept

Alefacept is a lymphocyte function-associated molecule 3/immunoglobulin G (LFA3-IgG1) fusion receptor protein, which functions by interfering with the CD2 receptor on T cells, causing apoptosis of effector memory T cells. By blocking LFA-3/CD2 interactions, alefacept can inhibit T-cell activation and proliferation. It has been approved for moderate to severe chronic plaque psoriasis and has no known nephrotoxicity. In addition, it has been used for the treatment of graft-versus-host disease in bone marrow transplantation [114]. In transplantation, a phase 2, multicenter, randomized, double-blind, placebo-controlled study in primary adult kidney transplant patients comparing alefacept, tacrolimus, and MMF to placebo, tacrolimus, and MMF was conducted. The primary endpoint was an incidence of biopsy-proven acute rejection at 6 months. No statistical differences between treatment arms were observed for the primary endpoint, patient or graft survival, as well as renal function. Alefacept was associated with statistically significant reduction in T memory lymphocyte subsets. Given that alefacept appears to react with a different population of T cells, i.e., effector memory T cells, rather than naïve T cells, it would seem that the results of this study are not surprising. There was an increased rate of malignancy in the alefacept group [115]. Alefacept may be better in models where memory T cells have a pathophysiologic role, e.g., sensitized or retransplant patients, GVHD after LTX. In fact, alefacept has been used successfully in such a case [116].

1.3.1.11 Signal 3 Inhibition

Tasocitinib

Tasocitinib (CP-690,550, tofacitinib) is an orally active immunosuppressant currently being tested for a variety of immune-mediated disorders, including prevention of transplant rejection. Tasocitinib specifically inhibits Janus-activated kinase 3 (JAK3), which is a hematopoietic cell-restricted tyrosine kinase involved in cytokine signal transduction associated with lymphocyte proliferation, specifically interfering with IL-2-mediated STAT5 activation in CD4+ T cells. A randomized pilot study compared two dosages of tasocitinib (15 mg BID and 30 mg BID, $n=20$ each) with tacrolimus ($n=21$) in de novo kidney allograft recipients [117]. Patients received anti-IL-2RA, MMF, and corticosteroids. The 6-month biopsy-proven acute

rejection rates were 5, 20, and 4.8 % for low- and high-dose tasocitinib and tacrolimus groups, respectively. The infectious complications were most frequent in the high-dose tasocitinib/MMF group with BK virus infection developing in 20 % and cytomegalovirus infection in 20 % of patients. Other side effects of tasocitinib included hyperlipidemia, anemia, and neutropenia. A larger study of tasocitinib in primary kidney transplantation utilized 15 mg BID for either 3 or 6 months followed by 10 mg BID thereafter and compared to a CsA control group – all groups were induced with anti-IL-2RA and given maintenance MPA and corticosteroids [118]. Of the 109 CsA patients, the ACR rate at 12 months was 18.8 % compared to longer high-dose tasocitinib ($n=106$) at 17.4 % and shorter high-dose tasocitinib ($n=107$) at 15.4 %. The finding that tasocitinib preserves regulatory T-cell function may be particularly important in LTX, as this may help to explain the immunologically privilege of LTX related to lack of chronic rejection and possible tolerance.

Anti-CD40 Ligand or Anti-CD40 Antibody

The CD40 molecule is expressed on antigen-presenting cells and serves as a costimulatory molecule through its interaction with CD154. Activation of CD40/CD154 has been shown to promote T-cell activation, B-cell proliferation and class switching, macrophage function, and a variety of other immunological processes. Page et al. have demonstrated that CD40- or CD40L-specific mAb could prevent and even reverse acute allograft rejection leading to prolongation of MHC-mismatched renal allografts in primates without the need of chronic maintenance immunosuppression [119]. Early studies with humanized anti-CD154 mAb were hampered by unexpected thromboembolic complications [120]. Further studies suggested that this was a function of the effects on integrin-binding sites on CD154 which are believed to aid in arterial plaque stabilization [121]. More recently, fully human anti-CD40 monoclonal antibodies, 4D11/ASKP1240, have been tested in a primate model with marked suppression of T-cell responses and prolongation of kidney allograft survival [122]. ASKP 1240 has recently undergone phase 1 evaluation, and currently phase 2a study is underway to assess the utility of ASKP1240 in MMF and CNI avoidant regiments (Basilixumab induction+ASKP1240+steroids+MMF vs Basilixumab+steroids+MMF+tacrolimus vs Basilixumab+ASKP1240+steroids +Tacrolimus) [123].

1.3.1.12 Chimerism

Tolerance

"Immunological tolerance," the state whereby the immune system fails to respond to a stimulus that would normally elicit an immunological response, is one of the "Holy Grails" of clinical transplantation. The ability to induce tolerance would obviate the need for maintenance immunosuppression and its long-term risks and associated complications as well as mitigate allograft rejection. The field of transplant tolerance was born in 1953 with the landmark report of Billingham, Brent, and Medawar where exposure during the fetal life of mice and chickens to homologous antigens leads to immunological tolerance. This was manifested by a lack of

response to skin grafting from the organism that was used in the inoculation process [124]. Subsequently, this neonatal tolerance has been demonstrated to be mediated through negative selection via mechanism(s) of thymic deletion of reactive T cells, also referred to as "central tolerance" [125]. However, similar approaches in adult recipients could not reproduce acceptance of donor tissues, unless the recipient had been cytoablated, in this early period, accomplished through lethal irradiation and reconstitution with donor bone marrow (radiation-induced chimerism) [126]. Chimerism refers to the development of an immune constitution that is comprised of cells of both donor and recipient lineages. In contrast to neonatally tolerant animals, the mechanism(s) of tolerance in these adult recipients involves not only clonal deletion but also active suppression [127].

Over the next 50 years, attempts were made in various animal models to induce tolerance with varying degrees of success, including early attempts of whole body and total lymphoid irradiation, shown to be necessary for the induction of immunological tolerance in bone marrow transplant patients. However, the development of potent immunosuppressive agents became the pathway to successful clinical solid organ transplantation. Because neither bone marrow nor any other kind of donor hematolymphopoietic cells were given adjunctively in solid organ transplantation, the enigmatic mechanisms of organ engraftment were assumed to be independent of leukocyte chimerism. However, there were clues that organ engraftment was a state of variable tolerance that in some cases became immunosuppression independent. Tolerance was inferred from a rapidly declining need for maintenance immunosuppression following the successful treatment of rejection. In addition, Starzl and coworkers demonstrated that long surviving allografts could be weaned from immunosuppression in a significant proportion of kidney and liver transplant recipients [128]. The finding that low-level multilineage donor leukocyte chimerism (microchimerism) was found in all tolerant patients and in one or more locations that included the skin, lymph nodes, heart, lungs, spleen, intestine, kidneys, bone marrow, and thymus emphasizes the importance of antigen migration and tolerance, as advocated by Starzl and Zinkernagel [129]. At any given site, the donor leukocytes were present in larger numbers in liver recipients than in kidney recipients studied at comparable posttransplant times. With the persistence of donor cells for as long as 30 years, it was inferred that the passenger leukocyte population of organ grafts was critical in establishing clinically operational tolerance. The migration of donor antigens, either as living cells or by shed alloantigens from the allograft, initiates a recipient immune response via direct or indirect antigen presentation pathways, respectively. Effector mechanisms include generation of cytotoxic T cells (CD8+) as well as downstream alloantibody as a result of CD4+ cytokines. As noted before, T-cell activation is essential for subsequent tolerance generation [130], and the use of potent immunosuppression is likely to delay or prevent the deletion of CD8+ effector T cells and the regulation of CD4+ helper T cells, likely mediated through apoptotic inducing clonal exhaustion as well as other peripheral tolerogenic pathways mediated through active suppressive regulation, such as T-regulatory cells (Treg) or myeloid-derived suppressor cells (MDSC). The liver allograft is naturally endowed with high levels of hepatic

stellate cells, Tregs, and MDSCs, which may facilitate the evolution to clinically operational tolerance [131].

The mechanism(s) by which tolerance is induced and maintained in clinical transplant recipients has been an area of ongoing investigation. A European consortium of liver transplant centers presented preliminary results of a prospective trial on 102 adult LTX recipients who were enrolled in a prospective immunosuppressive drug weaning study. A total of 41 recipients (40 %) were successfully weaned off immunosuppression a median to 11 years after LTX [132]. Similarly, in a pediatric recipient cohort receiving living donor liver allografts, a median of 7 years prior to enrollment in a prospective weaning protocol, 60 % of patients were successfully weaned [133], validating the earlier reports from the Kyoto University group of a 40 % success rate of weaning pediatric recipients of partial livers from parental donors from a steroid-sparing tacrolimus-based regimen [20]. While a variety of biomarkers have been associated with the development of clinical operational tolerance following LTX, including increased expression of hepatic iron homeostatic genes [21]; increased circulating CD4+, CD25+, CD127-, and FoxP3+ T-cell subsets [21]; and alterations in γδ1 T cells with an increased γδ1/γδ2 ratio [22], these preliminary results suggest that although the mechanism(s) associated with liver allograft tolerance are still being elucidated, obtaining success in clinically operational tolerance in liver transplantation is strictly related to the careful selection of the candidates for long-term weaning and follow-up [133–135].

The following are preliminary results of current tolerance studies, primarily being conducted in kidney transplants because of the requirement for preconditioning that is inherent with the requirement for donor-specific activation and deletion. Unfortunately, extrapolation of findings in the living donor scenario to deceased donors may prove to be a considerable barrier. To this point all successful attempts at tolerance have been accomplished by co-induction of hematopoietic chimerism. Induction of persistent mixed chimerism has been difficult to achieve in humans. Despite this, several studies have suggested that persistence of chimerism may not be necessary for the development of allograft tolerance. Scandling et al. published their cohort of 16 patients who underwent kidney transplantation with an induction protocol including ten doses of 80 cGy TBI each and five doses of rabbit ATG to human recipients of combined HLA-matched G-CSF "mobilized" blood mononuclear cell and kidney transplants from HLA-matched sibling donors. The hematopoietic grafts in the latter protocol were selected CD34+ cells with 1×10^6 CD3+ T cells/kg added back to the hematopoietic cells. Four patients developed persistent mixed chimerism, and eight developed transient chimerism [136]. All those with persistent mixed chimerism, and several of those with transient chimerism, were weaned from their maintenance immunosuppression. With these proofs of concept studies, the next challenge has been to attempt tolerance in HLA-mismatched transplant pairs. Kawai et al. followed up their initial study of myeloma patients with ten patients who received HLA-mismatched kidney transplants with an induction regiment consisting of thymic radiation, anti-CD2 mAb, and cyclophosphamide +/− rituximab followed by ~9 months of calcineurin inhibitors. Seventy percent of the patients were weaned

from all maintenance immunosuppression up to 5 years posttransplant, even though donor hematopoietic chimerism was transient [137].

Another approach to allograft tolerance has been the induction of full donor chimerism, whereby the recipients' immune constitution is replaced by that of the donor. Studies in the bone marrow transplant literature where full donor chimerism was induced have been plagued by high rates of GVHD and engraftment syndrome. Recently, attempts have been made with some success, to induce full donor chimerism in renal allograft recipients. In one of the largest groups to date, Leventhal et al. reported on 15 patients who underwent HLA-mismatched kidney transplantation after an induction regiment of pretreatment with fludarabine, 200-cGy TBI, and cyclophosphamide followed by infusion of tolerance-promoting CD8+, TCR-facilitating cell (FC)-based hematopoietic stem cell (HSC) graft infusion, and posttransplant immunosuppression with tacrolimus and mycophenolate mofetil. Postoperative monitoring for donor chimerism was used to establish decision for immunosuppressive drug weaning. Ten of these 15 patients have achieved durable full or mixed hematopoietic chimerism without GVHD or engraftment syndrome. Eight of these ten achieved durable, high-level (>90 %) hematopoietic chimerism. Six of the eight have successfully completed immunosuppression withdrawn without allograft rejection or graft loss (range of between 10 and 22 months off IS). The two remaining patients with high-level chimerism are currently undergoing immunosuppression withdrawal. Two subjects achieved sustained, mixed chimerism, while three participants achieved transient chimerism [138]. The key to this experience relies on the coadministration of the proprietary "facilitating cell" first identified by Ildstad and coworkers [139].

Todo and coworkers recently reported on their prospective liver tolerance study – they utilized a protocol of T-regulatory cell (Treg) expansion ex vivo to determine whether Treg-based cell therapy affords COT in living donor LT (LDLT). The group from Hokkaido University treated ten consecutive LDLT adult patients with Tregs created from peripheral blood mononuclear cells collected from both donors and recipients by leukapheresis and expanded ex vivo with a 2-week culture of recipient PBMNs with irradiated donor PBMNs under the presence of anti-CD80/anti-CD86 mAbs. These cells were infused into the recipient on postoperative day (POD) 13 along with cyclophosphamide given on POD 5. Steroids and MMF were stopped within 1 month, while the patients were left on tacrolimus monotherapy. At 6 months after LDLT, when graft function and histology were normal, immunosuppression was gradually tapered by spaced doses until it was discontinued 12 months later. Thus far, of the ten recipients, seven are free from immunosuppression [140] (update provided by Todo S. personal communication, April 2014). Protocols for deceased donor liver transplantation are planned.

Graft-Versus-Host Disease (GVHD)

The potential downside of facilitating increasing levels of chimerism is the prospect of developing GVHD, which is a rare but serious complication after liver transplantation. It occurs when immunocompetent donor lymphocytes transferred through the liver allograft become activated and are able to carry out an

immune response against recipient tissues. Acute GVHD is more commonly seen after hematopoietic stem cell transplantation and uncommonly after solid organ transplantation. The true incidence of GVHD after LT is not clear, but according to the more recent reports, it is estimated to be around 1–2 % [141]. GVHD usually presents with fever, skin rash, diarrhea, and pancytopenia 2–10 weeks after liver transplantation. The diagnosis is confirmed by demonstration of substantial number of donor chimerism in the patient's peripheral blood. Studies have shown that these donor chimeric cells are usually CD8+ T cells [142]; however, multilineage donor hematopoietic chimerism has also been described [143–145]. Despite a variety of protocols for treatment of GVHD after LT, with different strategies to decrease or increase immunosuppression [141, 142, 145–147], response rate remains poor with 85 % mortality rate in affected patients. Mortality is usually as a result of multiorgan failure and especially bone marrow failure and infection. To date, only two forms of therapy have been successful, reprogramming the recipient's immune system with infusion of pre-transplant recipient bone marrow [148] and the promising use of alefacept, a fusion protein comprising the extracellular CD2-binding portion of the human leukocyte function antigen-3 (LFA-3) linked to the Fc portion of human-IgG1, and selectively targets memory T cells [149].

1.4 Conclusions

The field of transplant immunology and its applications in clinical transplant has undergone remarkable changes in the last 50 years. With the development and refinement in our understanding of the process underlying clinical transplantation, the ability to prolong graft survival has vastly improved. Despite these advances, long-term graft failure remains a significant problem. Additionally, many of our current immunosuppressants continue to have significant side effect profiles. Optimizing efficacy and decreasing toxicity of regiments continue to drive the efforts toward more efficacious and less toxic regiments. Coupled with new advances in immunological understanding, the field of transplantation continues its quest toward immunosuppressant optimization and even elimination, to improve the lives of the increasing number of transplant recipients.

References

1. Snell GD. Methods for the study of histocompatibility genes. J Genet. 1948;49:87–108.
2. Brent L. A history of transplantation immunology. San Diego: Academic; 1997.
3. Merrill JP, Murray JE, Harrison JH, et al. Successful homotransplantation of the kidney between non-identical twins. N Engl J Med. 1960;262:1251–60.
4. Rogers BO. The relation of immunology to tissue homotransplantations. Ann N Y Acad Sci. 1955;59:277–466.
5. Lepez T, Vandewoestyne M, Deforce D. Fetal microchimeric cells in blood and thyroid glands of women with autoimmune thyroid disease. Chimerism. 2012;3:21–3.

6. Matsuoka K, Inchinohe T, Hashimoto D, Asakura S, Tanimoto M, Teshima T. Fetal tolerance to maternal antigens improves the outcome of allogeneic bone marrow transplantation by a CD4+, CD25+ T-cell-dependent mechanism. Blood. 2006;107:404–9.
7. Leveque L, Khosrotehrani K. Can maternal microchimeric cells influence the fetal response toward self-antigens? Chimerism. 2011;2:71–7.
8. Sivaganesh S, Harper S, Conlon T, Callaghan C, Saeb-Parsi K, Neus M, Motallebzadeh R, Bolton E, Bradley J, Pettigrew G. Copresentation of intact and processed MHC alloantigen by recipient dendritic cells enables delivery of linked help to alloreactive CD8 T cells by indirect-pathway CD4 T cells. Immunology. 2013;190(11):5829–38.
9. Rifle G, Mousson C, Martin L, Guignier F, Hajji K. Donor-specific antibodies in allograft rejection: clinical and experimental data. Transplantation. 2005;79(3 Supp):S14–8.
10. Mengel M, Husain S, Hidalgo L, Sis B. Phenotypes of antibody-mediated rejection in organ transplants. Transpl Int. 2012;25(6):611–22.
11. Palanki M. Inhibitors of AP-1 and NF-κB mediated transcriptional activation: therapeutic potential in autoimmune disease and structural diversity. Curr Med Chem. 2002;9(2):219–27.
12. Guy C, Vignali D. Organization of proximal signal initiation at the TCR: CD3 complex. Immunol Rev. 2009;232(1):7–21.
13. Manicassamy S, Gupta S, Sun Z. Selective function of PKC-θ in T cells. Cell Mol Immunol. 2006;3(4):263–70.
14. Dure M, Macian F. IL-2 signaling prevents T-cell anergy by inhibiting the expression of anergy-inducing genes. Mol Immunol. 2009;46(5):999–1006.
15. Bellini A, Marini M, Biachetti L, Barcztk M, Schmidt M, MattoIi S. Interleukin (IL)-4, IL-13 and IL17A differentially affect the profibrotic and proinflammatory functions of fibrocytes from asthmatic patients. Mucosal Immunol. 2012;5(2):140–9.
16. Maynihan B, Tolloczko B, El Bassam S, Ferraro P, Michoud M. IFN-gamma, IL-4 and IL-13 modulate responsiveness of human airway smooth muscle cells to IL-13. Respir Res. 2008;9:84.
17. Baracho G, Cato M, Zhu Z, Jaren OR, Hobeika E, Reth M, Rickert R. PDK1 regulates B cell differentiation and homeostasis. Proc Natl Acad Sci. 2014;111(26):9573–8.
18. Valenzuela NM, McNamara JT, Reed EF. Antibody-mediated graft injury: complement-dependent and complement-independent mechanisms. Curr Opin Organ Transplant. 2014;19(1):33–40. doi: 10.1097/MOT.0000000000000040.
19. Wilkinson A. Protocol transplant biopsies: are they really needed? Clin J Am Soc Nephrol. 2006;1(1):130–7.
20. Kaech S, Cui W. Transcriptional control of effector and memory CD8+ T cell differentiation. Nat Rev Immunol. 2012;12(11):749–61.
21. Abbas A, Lichtman A, Pillai S. Basic immunology: functions and disorders of the immune system. Chapter 6. Philadelphia: Saunders; 2014. p. 117–30.
22. Morris P, Knechtle S, Nankivell BJ. Kidney transplant: principles and practices. Chapter 27. Philadelphia: Saunders; 2014. p. 411–34.
23. Paul LC, Hayry P, Foegh M, Dennis MJ, et al. Diagnostic criteria for chronic rejection/accelerated allograft atherosclerosis in heart and kidney transplants: joint proposal from the fourth Alexis Carrel conference on chronic rejection and accelerated arteriosclerosis in transplanted organs. Transplant Proc. 1993;25:2022–3.
24. Halloran PF, Melf A, Barth C. Rethinking chronic allograft nephropathy: the concept of accelerated senescence. J Am Soc Nephrol. 1999;10:167–81.
25. Schwartz R, Stack J, Dameshek W. Effects of 6-mercaptopurine on antibody production. Proc Soc Exp Sci Med. 1958;99(1):164–7.
26. Clane RY. The rejection of renal homografts: inhibition in dogs with 6-mercaptopurine. Lancet. 1960;1(7121):417–8.
27. Kahan BD. Toward a rational design of clinical trends in immunosuppressive agents in transplantation. Immunol Rev. 1993;136:29–49.
28. Kung L, Gourishankar S, Halloran PF. Molecular pharmacology of immunosuppressive agents in relation to their clinical use. Curr Opin Organ Transplant. 2000;5:268–75.

29. Chan GL, Erdmann GR, Gruber SA, et al. Azathioprine metabolism: pharmacokinetics of 6-mercaptopurine, 6-thiouric acid and 6-thioguanine nucleotides in renal transplant patients. J Clin Pharmacol. 1990;30:358.
30. Lia-no F, Moreno A, Matesanz R, et al. Veno-occlusive hepatic disease of the liver in renal transplantation: is azathioprine the cause? Nephron. 1989;51:509.
31. Frick TW, Fryd DS, Goodale RL, et al. Lack of association between azathioprine and acute pancreatitis in renal. Lancet. 1991;337:251.
32. Stamp LK, Chapmann PT. Gout and organ transplantation. Curr Rheumatol Rep. 2012;14(2):165–72.
33. Sollinger HW. For the US renal transplant mycophenolate mofetil study group. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. Transplantation. 1995;60:225–32.
34. European Mycophenolate Mofetil Cooperative Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporine and corticosteroids for prevention of acute rejection. Lancet. 1995;345:1321–5.
35. McDiarmid SV. Mycophenolate mofetil in liver transplantation. Clin Transplant. 1996;10:140–5.
36. Pescovitz MA. For the mycophenolate mofetil acute renal rejection study group. Mycophenolate mofetil for the treatment of a first acute renal allograft rejection. Transplantation. 1998;65:235–341.
37. Mele TS, Halloran PF. The use of mycophenolate mofetil in transplant recipients. Immunopharmacology. 2000;47:215–45.
38. Meulen CG, Wetzels FM, Hilbrands LB. The influence of mycophenolate mofetil on the incidence and severity of primary cytomegalovirus infections and disease after renal transplantation. Nephrol Dial Transplant. 2000;15:711–4.
39. Leray C, Coulomb A, Elefant E, Frydman R, Audibert F. Mycophenolate mofetil in pregnancy after renal transplantation: a case of major fetal malformations. Obstet Gynecol. 2004;103:1091–4.
40. Tornatore KM, Reed KA, Venuto RC. Methylprednisolone and cortisol metabolism during the early post-renal transplant period. Clin Transplant. 1995;9:427.
41. Adcock IM. Molecular mechanisms of glucocorticoid actions. Pulm Pharmacol Ther. 2000;13:115–26.
42. Boitard C, Bach JF. Long-term complications of conventional immunosuppressive treatment. Adv Nephrol. 1989;18:335.
43. Freeman DJ. Pharmacology and pharmacokinetics of cyclosporine. Clin Biochem. 1991;24:9.
44. Levy G, Grant D. Potential for CsA-Neoral in organ transplantation. Transplant Proc. 1994;26:2932.
45. Kovarik JM, Mueller EA, van Bree JB, et al. Cyclosporine pharmacokinetics and variability from a microemulsion formulation – a multicenter investigation in kidney transplant patients. Transplantation. 1994;58:658.
46. Watkins PB. The role of cytochromes P-450 in cyclosporine metabolism. J Am Acad Dermatol. 1990;23:1301.
47. Screiber SL, Crabtree GR. The mechanism of action of cyclosporine A and FK506. Immunol Today. 1992;13:136–42.
48. Pankewycz OG. Transforming growth factor-β and renal graft fibrosis. Curr Opin Organ Transplant. 2000;5:336–42.
49. Remuzzi G, Bertani T. Renal vascular and thrombotic effects of cyclosporine. Am J Kidney Dis. 1989;13:261.
50. Rush DN. Cyclosporine toxicity to organs other than the kidney. Clin Biochem. 1991;24:101.
51. Luke RG. Mechanism of cyclosporine-induced hypertension. Am J Hypertens. 1991;4:468.
52. Reznick VM, Lyons Jones K, Durham BL, et al. Changes in facial appearance during cyclosporine treatment. Lancet. 1987;1:1405.
53. Fung JJ, Todo S, Jain A, et al. Conversion from cyclosporine to FK506 in liver allograft recipients with cyclosporine related complications. Transplant Proc. 1990;22:6–12.
54. Fung JJ, Jain A, Hamad I, et al. Long term effects of FK506 following conversion from cyclosporine to FK506 for chronic rejection in liver transplant recipients. Hepatology. 1993;18:74A.

55. Sher LS, Cosenza CA, Michel J, et al. Efficacy of tacrolimus as rescue therapy for chronic rejection in orthotopic liver transplantation: a report of the U.S. Multicenter Liver Study Group. Transplantation. 1997;64:258.
56. Fung J, Eliasziw M, Todo S, et al. The Pittsburgh randomized trial of tacrolimus compared to cyclosporine for hepatic transplantation. J Am Coll Surg. 1996;183:117.
57. The European FK506 Multicenter Liver Study Group. Randomized trial comparing tacrolimus and cyclosporine in prevention of liver allograft rejection. Lancet. 1994;334:423.
58. The United States Multicenter FK506 Liver Study Group. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression in liver transplantation. N Engl J Med. 1994;331:1110.
59. Jordan ML, Naraghi R, Shapiro R, et al. Tacrolimus rescue therapy for renal allograft rejection – five year experience. Transplantation. 1997;63:436.
60. FK506 Kidney Transplant Study Group. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric kidney transplantation. Transplantation. 1997;63:977–83.
61. Mayer AD, Dmitrewski J, Squifflet JP, et al. Multicenter randomized trial comparing tacrolimus and cyclosporine in the prevention of renal allograft rejection. A report of the European tacrolimus multicenter renal study group. Transplantation. 1997;64:436.
62. Mentzer RM, Jahania MS, Lasley RD. Tacrolimus as a rescue immunosuppressant after heart and lung transplantation. The U.S. Multicenter FK506 Study Group. Transplantation. 1998; 65:109.
63. Corry RJ, Egidi MF, Shapiro R, et al. Tacrolimus without antilymphocyte induction therapy prevents pancreas loss from rejection in 123 consecutive patients. Transplant Proc. 1998; 30:521.
64. Gruessner RWG, Tacrolimus Pancreas Transplant Study Group. Tacrolimus in pancreas transplantation: a multicenter analysis. Clin Transpl. 1997;11:299.
65. Regazzi MB, Rinaldi M, Molinaro M, et al. Clinical pharmacokinetics of tacrolimus in heart transplant recipients. Ther Drug Monit. 1999;21:2–7.
66. Venkataramanan R, Jain A, Warty VS, et al. Pharmacokinetics of FK506 in transplant patients. Transplant Proc. 1992;23:2736–40.
67. Warty VS, Venkataramanan R, Zendehrouh P, et al. Practical aspects of FK506 analysis (Pittsburgh experience). Transplant Proc. 1992;23:2730–1.
68. Cillo U, Alessiani M, Fung JJ, et al. Major adverse effects of FK506 used as an immunosuppressive agent after liver transplantation. Transplant Proc. 1993;25:628–34.
69. Considine A, Tredger JM, Heneghan M, Agarwal K, Samyn M, Heaton ND, O'Grady JG, Aluvihare VR. Performance of modified-release tacrolimus after conversion in liver transplant patients indicates potential favourable outcomes in selected cohorts. Liver Transpl. 2014; 21(1):29–37.
70. Moutabarrik A, Ishibashi M, Kameoka H, et al. FK506 mechanism of nephrotoxicity: stimulatory effect on endothelin secretion by cultured kidney cells. Transplant Proc. 1992; 23:3133–6.
71. Eidelman BH, Abu-Elmagd K, Wilson J, et al. Neurologic complications of FK506. Transplant Proc. 1991;23:3175–8.
72. Kung PC, Goldstein G, Reinherz EL, Schlossman SF. Monoclonal antibodies defining distinctive human T cell surface antigens. Science. 1979;206:347–9.
73. Reinherz EL, Meuer S, Fitzgeral KA, Hussey RE, Levine H, Schlossman SF. Antigen recognition by human T lymphocytes is linked to surface expression of the T3 molecular complex. Cell. 1982;30:735–43.
74. Van den Elsen P, Shepley B-A, Borst J, et al. Isolation of cDNA clones encoding 20K T3 glycoprotein of human T-cell receptor complex. Nature. 1984;312:413–8.
75. Van Wauwe JP, De Mey JR, Goossens JG. OKT3: a monoclonal anti-human T lymphocyte antibody with potent mitogenic properties. J Immunol. 1980;124:2708–13.
76. Chang TW, Kung PC, Gingras SP, Goldstein G. Does OKT3 monoclonal antibody react with an antigen-recognition structure on human T cells? Proc Natl Acad Sci U S A. 1981;78:1805–8.

77. Landergren U, Ramstedt U, Axberg I, Ullberg M, Jondal M, Wigzell H. Selective inhibition of human T cell cytotoxicity at levels of target recognition or initiation of lysis by monoclonal OKT3 and Leu-2a antibodies. J Exp Med. 1982;155:1579–84.
78. Biddison WE, Rao PE, Talle MA, Goldstein G, Shaw S. Possible involvement of OKT3 molecule in T cell recognition of class II HLA antigens: evidence from studies of cytotoxic T lymphocytes specific for SB antigens. J Exp Med. 1982;156:1065–76.
79. Chatenoud L, Baudrihaye MF, Kreis H, et al. Human in vivo antigenic modulation induced by the anti-T cell OKT3 monoclonal antibody. Eur J Immunol. 1982;12:979–82.
80. Giorgi JV, Cosimi AB, Colvin RB, Goldstein G, Delmonico FL, Russell PS. Monitoring immunosuppression following renal transplantation. Diagn Immunol. 1983;1:174–8.
81. Jaffers GJ, Colvin RB, Cosimi AB, et al. The human immune response to murine OKT3 monoclonal antibody. Transplant Proc. 1983;15:646–8.
82. Chatenoud L, Baudrihaye MF, Chkoff N, Kreis H, Bach JF. Immunologic follow-up of renal allograft recipients treated prophylactically by OKT3 alone. Transplant Proc. 1983;15: 643–5.
83. Genestier L, Fournel S, Flacher M, Assossou O, Revillard JP, Bonnefoy-Berard N. Induction of Fas (Apo-1, CD95)-mediated apoptosis of activated lymphocytes by polyclonal antithymocyte globulins. Blood. 1998;91:2360–8.
84. Thiyagarajan UM, Ponnuswamy A, Bagul A. Thymoglobulin and its use in renal transplantation: a review. Am J Nephrol. 2013;37:586–601.
85. Brennin DC, Daller JA, Lake KD, Cibrik D, Del Castillo D. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. N Engl J Med. 2006;355:1967–77.
86. Brennan DC, Schnitzler MA. Long term results of rabbit antithymocyte globulin and basiliximab induction. N Engl J Med. 2008;359:1736–8.
87. Ramirez CB, Dorai C, di Fracesco F, Iaria M, Kang Y, Marino IR. Basiliximab induction in adult liver transplant recipients with 93% rejection-free patient and graft survival at 24 months. Transplant Proc. 2006;38(10):3633–5.
88. Turner AP, Knechtle SJ. Induction immunosuppression in liver transplantation: a review. Transpl Int. 2013;26(7):673–83.
89. Kovarik JM, Gridelli BG, Martin S, Rodeck B, Melter M, Dunn SP, et al. Basiliximab in pediatric liver transplantation: a pharmacokinetic-derived dosing algorithm. Pediatr Transplant. 2002;6:224–30.
90. Neuberger JM, Mamelok RD, Neuhaus P, Pirenne J, Samuel D, Isoniemi H, Rostaing L, Rimola A, Marshall S, Mayer AD, ReSpeCT Study Group. Delayed introduction of reduced-dose tacrolimus, and renal function in liver transplantation: the 'ReSpECT' study. Am J Transplant. 2009;9(2):327–36.
91. Guttmann RD, Caudrelier P, Alberici G, Touraine JL. Pharmacokinetics, foreign protein immune response, cytokine release, and lymphocyte subsets in patients receiving thymoglobulin and immunosuppression. Transplant Proc. 1997;29:24–6.
92. Miller RA, Maloney DG, McKillop J, Levy R. In vivo effects of murine hybridoma monoclonal antibody in a patient with T-cell leukemia. Blood. 1981;58:78–86.
93. Lehman JA, Calvo C, Gomez-Cambronero J. Mechanism of ribosomal p70s6 Kinase activation by granulocyte macrophage colony-stimulating factor in neutrophils: cooperation of a MEK-related, THR421/SER424 kinase and a rapamycin-sensitive, m-TOR-related THR389 kinase. J Biol Chem. 2003;278(30):28130–8.
94. Brattstrom C, Tyden G, Sawe J, Herlenius G, Claesson K, Groth CG. A randomized, double-blind, placebo-controlled study to determine safety, tolerance, and preliminary pharmacokinetics of ascending single doses of orally administered sirolimus (rapamycin) in stable renal transplant recipients. Transplant Proc. 1996;28(2):985–6.
95. Ponticelli C. The pros and the cons of mTOR inhibitors in kidney transplantation. Expert Rev Clin Immunol. 2014;10(2):295–305.
96. Podder H, Stepkowski SM, Napoli KL, Clark J, Verani RR, Chou TC, Kahan BD. Pharmacokinetic interactions augment toxicities of sirolimus/cyclosporine combinations. J Am Soc Nephrol. 2001;12(5):1059–71.

97. Kahn J, Muller H, Iberer F, Kniepeiss D, Duller D, Rehak P, Tscheliessnigg K. Incisional hernia following liver transplantation. Incidence and predisposing risk factors. Clin Trans. 2007; 21(3):423–6; Sollinger HW, Deierhoi MH, Belzer FO, et al. RS-61433: a phase I clinical trial and pilot rescue study. Transplantation. 1992;30:358.
98. Tiong HY, Flechner SM, Zhohu L, Wee A, Mastroianni B, Savas K, Goldfarb D, Derweesh I, MOdlin C. A systematic approach to minimizing wound problems for de novo sirolimus-treated kidney transplant recipients. Transplantation. 2009;87(2):296–302.
99. Budde K, Becker T, Arns W, Sommerer C, Reinke P, Eisenberger U, et al. Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplant: an open-label, randomized, controlled trial. Lancet. 2011;377(9768):837–47.
100. Saliba F, De Simone P, Nevens F, De Carlis L, Metslaar HJ, Beckebaum S, et al. Renal function at two years in liver transplant patients receiving everolimus: results of a randomized, multicenter study. Am J Transplant. 2013;13:1734–45.
101. Duvoux C, Saliba F, Kaiser G, De Carlis L, Metselaar H, De Simone P, Nevens F, Fischer L, Fung J, Dong G, Rauer B, Junge G. Efficacy and safety of everolimus with reduced tacrolimus in *de novo* liver transplant recipients: long term results from the H2304E1 study. Am J Transplant. 2014;14(S3):709. Abstract A430.
102. Waid TH, Lucas BA, Thompson JS, McKeown JW, Brown S, Kryscia R, Skeeters LJ. Treatment of renal allograft rejection with T10B9.1A31 or OKT3: final analysis of a phase II clinical trial. Transplantation. 1997;64(2):274–81.
103. Budde K, Sommerer C, Becker T, Asderakis A, Pietruck F, Grinyo JM, Rigotti P, Dantal J, Ng J, Barten MJ, Weber M. Sotrastaurin, a novel small molecule inhibiting protein kinase C: first clinical results in renal-transplant recipients. Am J Transplant. 2010;10(3):571–81.
104. Friman S, Arns W, Nashan B, Vicenti F, Banas B, Budde K, Cibrik D, Chan L, Klempnauer J, Mulgaonkar S, Nicholson M, Wahlberg J, Wissing KM, Abrams K, Witte S, Woodle ES. Sotrastaurin, a novel small molecule inhibiting protein-kinase C: randomized phase II study in renal transplant recipients. Am J Transplant. 2011;11(7):1444–55.
105. Russ GR, Tedesco-Silva H, Kuypers DR, Cohney S, Langer RM, Witzke O, Eris J, Sommerer C, von Zur-Muhlen B, Woodle ES, Gill J, Ng J, Klupp J, Chodoff L, Budde K. Efficacy of sotrastaurin plus tacrolimus after de novo kidney transplantation: randomized, phase II trial results. Am J Transplant. 2013;13(7):1746–56.
106. Vicenti F, Larsen C, Durrbach A, Werkerle T, Nashan B, Blancho G, Lang P, Grinyo J, Halloran PF, et al. Costimulation blockade with belatacept in renal transplantation. N Engl J Med. 2005;353(8):770–81.
107. Grinyo J, Alberu J, Contieri FL, Manfro RC, Mondragon G, Nainan G, Rial Mdel C, Steinberg S, Vicenti F, Dong Y, et al. Improvement in renal function in kidney transplant recipients switched from cyclosporine or tacrolimus to belatacept: 2-year results from the long-term extension of a phase II study. Transpl Int. 2012;25(10):1059–64.
108. Vicenti F, Charpentier B, Vanreterghem Y, Rostaing L, Bresnahan B, Darji P, Massari P, Mondragon-Ramirez GA, Agarwal M, DiRusso G, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT Study). Am J Transplant. 2010;10(3):535–46.
109. Pestana JO, Grinyo J, Vanrenterghem Y, Becker T, Campistol JM, Florman S, Garcia VD, Kamar D, Lang P, Manfro RC, et al. Three-year outcomes from BENEFIT-EXT: a phase III study of belatacept versus cyclosporine in recipients of extended criteria donor kidneys. Am J Transplant. 2012;12(3):630–9.
110. Klintmalm GB, Feng S, Lake JR, Vargas HE, Wekerle T, Agnes S, Brown KA, Nashan B, Rostaing L, Meadows-Shropshire S, et al. Belatacept-based immunosuppression in de novo liver transplant recipients: 1-year experience from a phase II randomized study. Am J Transplant. 2014;14(8):1817–27.
111. Vicenti F, Mendez R, Pescovitz M, Rajagopalan PR, Wilkinson AH, Butt K, Slakey DP, Lorber MI, Garg JP, Garovoy M. A phase I/II randomized open-label multicenter trial of efalizumab, a humanized anti-CD11a, anti-LFA-1 in renal transplantation. Am J Transplant. 2007;7(7):1770–7.

112. Efalizumab (marketed as Raptiva) Information. FDA Announcement: Postmarket Drug Safety Information for Patients and Providers. Accessed 6/6/2015 (http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm133337.htm).
113. Shapira MY, Resnick IB, Bitan M, Ackerstein A, Tsirigotis P, Gesundheit B, Zilberman I, Miron S, Leubovic A, Slavin S, Or R. Rapid response to alefacept given to patients with steroid resistant or steroid dependent acute graft-versus: a preliminary report. Bone Marrow Transplant. 2005;36(12):1097–101.
114. Rostaing L, Charpentier B, Glyda M, Rigotti P, Hettich F, Franks B, Houbiers JG, First R, Holman JM. Alefacept combined with tacrolimus, mycophenolate mofetil and steroids in de novo kidney transplantation: a randomized controlled trial. Am J Transplant. 2013;13(7):1724–33.
115. Stotler CJ, Eghtesad B, Hsi E, Silver B. Rapid resolution of GVHD after orthotopic liver transplantation in a patient treated with alefacept. Blood. 2009;113(21):3565–6.
116. Busque S, Leventhal J, Brennan DC, Steinberg S, Klintmalm G, Shah T, et al. Calcineurin-inhibitor-free immunosuppression based on JAK inhibitor CP-690, 550: a pilot study in de novo kidney allograft recipients. Am J Transplant. 2009;9(8):1936–45.
117. Vincenti F, Tedesco Silva H, Busque S, O'Connell P, Friedewald J, Cibrik D, et al. Randomized phase 2b trial of tofacitinib (CP-690, 550) in de novo kidney transplant patients: efficacy, renal function and safety at 1 year. Am J Transplant. 2012;12(9):2446–56.
118. Page A, Srinivasan S, Singh K, Russell M, Hamby K, Deane T, Sen S, Stempora L, Leopardi F, Price AA, et al. CD40 blockade combines with CTLA4Ig and sirolimus to produce mixed chimerism in an MHC-defined rhesus macaque transplant model. Am J Transplant. 2012;12(1):115–25.
119. Buhler L, Alwayn IP, Appel 3rd JZ, Robson SD, Cooper DK. AntiCD-154 monoclonal antibody and thromboembolism. Transplantation. 2001;71(3):491.
120. Andre P, Prasad KS, Denis CV, He M, Papalia JM, Hynes RO, et al. CD40 stabilizes arterial thrombi by a beta3 integrin- dependent mechanism. Nat Med. 2002;8:247–52.
121. Aoyagi T, Yamashita K, Suzuki T, Uno M, Goto R, Taniguchi M, et al. A human anti-CD40 monoclonal antibody, 4d11, for kidney transplantation in cynomolgus monkeys: induction and maintenance therapy. Am J Transplant. 2009;9(8):1732–41.
122. A study to assess the efficacy and safety of ASKP1240 in de Novo Kidney transplant recipients. https://clinicaltrials.gov/ct2/show/NCT01780844?term=ASKP+1240&rank=4.
123. Billingham RE, Brent L, Medawar PB. Activity acquired tolerance of foreign cells. Nature. 1953;172:603–6.
124. Spitzer TR, Sykes M, Tolkoff-Rubin N, Kawai T, McAfee SL, Dey BR, et al. Long-term follow-up of recipients of combined human leukocyte antigen-matched bone marrow and kidney transplantation for multiple myeloma with end-stage renal disease. Transplantation. 2011;91(6):672–6.
125. Morrissey PJ, Sharrow SO, Kohno Y, Berzofsky JA, Singer A. Correlation of intrathymic tolerance with intrathymic chimerism in neonatally tolerized mice. Transplantation. 1985;40:68–72.
126. Main JM, Prehn RT. Successful skin homografts after the administration of high dosage X radiation and homologous bone marrow. J Natl Cancer Inst. 1955;15:1023–9.
127. Streilein JW, Gruchalla RS. Analysis of neonatally induced tolerance to H-2 alloantigens: I. Adoptive transfer indicates that tolerance of class I and class II antigens is maintained by distinct mechanisms. Immunogenetics. 1981;12:161–73.
128. Starzl TE, Demetris AJ, Trucco M, Murase N, Ricordi C, Ildstad S, Ramos H, Todo S, Tzakis A, Fung JJ, Nalesnik M, Zeevi A, Rudert WA, Kocova M. Cell migration and chimerism after whole-organ transplantation: the basis of graft acceptance. Hepatology. 1993;17:1127–52.
129. Starzl TE, Zinkernagel R. Antigen localization and migration in immunity and tolerance. N Engl J Med. 1998;339:1905–13.
130. Li Y, Li XC, Zheng XX, Wells AD, Turka LA, Strom TB. Blocking both signal 1 and signal 2 of T-cell activation prevents apoptosis of alloreactive T cells and induction of peripheral allograft tolerance. Nat Med. 1999;5(11):1298–302.

131. Charles R, Lu L, Qian S, Fung JJ. Stromal cell-based immunotherapy in transplantation. Immunotherapy. 2011;3(12):147–85.
132. Benítez C, Londoño MC, Miquel R, Manzia TM, Abraldes JG, Lozano JJ, Martínez-Llordella M, López M, Angelico R, Bohne F, Sese P, Daoud F, Larcier P, Roelen DL, Claas F, Whitehouse G, Lerut J, Pirenne J, Rimola A, Tisone G, Sánchez-Fueyo A. Prospective multicenter clinical trial of immunosuppressive drug withdrawal in stable adult liver transplant recipients. Hepatology. 2013;58(5):1824–35.
133. Feng S, Ekong UD, Lobritto SJ, Demetris AJ, Roberts JP, Rosenthal P, Alonso EM, Philogene MC, Ikle D, Poole KM, Bridges ND, Turka LA, Tchao NK. Complete immunosuppression withdrawal and subsequent allograft function among pediatric recipients of parental living donor liver transplants. JAMA. 2012;307(3):283–93.
134. Ramos HC, Reyes J, Abu-Elmagd K, Zeevi A, Reinsmoen N, Tzakis A, Demetris AJ, Fung JJ, Flynn B, McMichael J, Ebert F, Starzl TE. Weaning of immunosuppression in long-term liver transplant recipients. Transplantation. 1995;59(2):212–7.
135. Lerut J, Sanchez-Fueyo A. An appraisal of tolerance in liver transplantation. Am J Transplant. 2006;6:1774–80.
136. Scandling JD, Busque S, Dejbakhsh-Jones S, Benike C, Sarwal M, Millan MT, et al. Tolerance and withdrawal of immunosuppressive drugs in patients given kidney and hematopoietic cell transplants. Am J Transplant. 2012;12(5):1133–45.
137. Kawai T, Cosimi AB, Spitzer TR, et al. HLA-mismatched renal transplantation without maintenance immunosuppression. N Engl J Med. 2008;358(4):353–61.
138. Leventhal J, Abecassis M, Miller J, Gallon L, Tollerud D, Elliot MJ, et al. Tolerance induction in HLA disparate living donor kidney transplantation by donor stem cell infusion: durable chimerism predicts outcome. Transplantation. 2013;95:169–76.
139. Kaufman CL, Colson YL, Wren SM, Watkins S, Simmons RL, Ildstad ST. Phenotypic characterization of a novel bone marrow-derived cell that facilitates engraftment of allogeneic bone marrow stem cells. Blood. 1994;84:2436–46.
140. Todo S, Yamashita K. Operational tolerance by a regulatory T cell-based cell therapy in living liver transplantation: a preliminary report. Exp Clin Transplant. 2013;11 Suppl 2:9.
141. Taylor AL, Gibbs P, Bradley JA. Acute graft versus host disease following liver transplantation: the enemy within. Am J Transplant. 2004;4:466–74.
142. Domiati-Saad R, Klintmalm GB, Netto G, Agura ED, Chinnakotla S, Smith DM. Acute graft versus host disease after liver transplantation: patterns of lymphocyte chimerism. Am J Transplant. 2005;5:2968–73.
143. Mark W, Ollinger R, Rumpold H, Wolf D, Nachbaur D, Aigner F, Margreiter C, Gassner C, Schennach H, Graziadei I, Vogel W, Margreiter R, Gunsilius E. The liver graft as Trojan horse-multilineage donor-derived hematopoiesis after liver transplantation: case report. Transplant Proc. 2013;45(9):3438–41.
144. Collins Jr RH, Anastasi J, Terstappen LW, Nikaein A, Feng J, Fay JW, Klintmalm G, Stone MJ. Brief report: donor-derived long-term multilineage hematopoiesis in a liver-transplant recipient. N Engl J Med. 1993;328(11):762–5.
145. Chen X-B, Yang J, Ming-Qing X, Wen T-F, Lu-Nan Y. Unsuccessful treatment of four patients with acute graft-vs -host disease after liver transplantation. World J Gastroenterol. 2012;18(1):84–9.
146. Perri R, Assi M, Talwalkar J, Heimbach J, Hogan W, Moore SB, Rosen CB, Graft VS. Host disease after liver transplantation: a new approach is needed. Liver Transpl. 2007;13:1092–9.
147. Chinnakotla S, Smith DM, Domiati-Saad R, Agura ED, Watkins DL, Netto G, Uemura T, Sanchez EQ, Levy MF, Klintmalm GB. Acute graft-versus-host disease after liver transplantation: role of withdrawal of immunosuppression in therapeutic management. Liver Transpl. 2007;13:157–61.
148. Ricordi C, Tzakis AG, Zeevi A, Rybka WB, Demetris AJ, Fontes P, Nalesnik MA, Trucco M, Ukah FO, Ball ED, Mullen EE, Marino IR, Fung J, Starzl TE. Reversal of graft-versus-host disease with infusion of autologous bone marrow. Cell Transplant. 1994;3(2):187–92.
149. Stotler CJ, Eghtesad B, His E, Silver B. Rapid resolution of GVHD after orthotopic liver transplantation in a patient treated with alefacept. Blood. 2009;113:5365–6.

Infection Complications After Abdominal Organ Transplantation

2

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2.1 Introduction

Infection is a leading cause of morbidity and mortality after solid organ transplantation (SOT) [1]. Patients undergoing abdominal organ transplantation (AOT) share most risk factors for infection with the other types of transplant recipients (see Table 2.1). However, there are some unique risk factors related to underlying disease, surgical complexity, and immunosuppression used in the AOT.

Urinary tract infection is the most common infectious complication after renal transplantation [2]. After the procedure, urine flow alterations may develop because of ureteral stenosis or vesicoureteral reflux. In addition, some renal transplant patients have underlying urological abnormalities (e.g., neurogenic bladder or chronic vesicoureteral reflux) that increase the risk of posttransplant urinary tract infection. Renal transplantation from cardiac death donors develop delayed graft function more frequently than other types of renal transplantation, which in turn increases the need for dialysis and the incidence of infection [2].

Living donor and cardiac death donor liver transplantations have an increased risk of biliary complications and ischemic cholangiopathy which increases the risk of bile infections [3, 4]. Bile reconstructions other than duct to duct carry a higher risk of bile infections and peritonitis [5].

Regarding pancreas transplantation, bladder drainage is associated with a higher risk of infection than intestinal drainage [6]. As pancreas transplantation involves intestinal manipulation, the risk of peritonitis and abdominal collections is high.

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Table 2.1 Risk assessment in transplantation

Greater infectious risk
Critical illness entering transplantation
Prior colonization with antimicrobial-resistant pathogens
Induction therapy – lymphocyte depletion
High-dose corticosteroids
Plasmapheresis (not well studied)
High rejection risk (HLA mismatch desensitization)
Early graft rejection
Graft dysfunction
Technical complications
Anastomotic leak
Bleeding
Wound infection/poor wound healing
Prolonged intubation/intensive unit care
Surgical, vascular, or urinary catheters
Lower infectious risk
Immunologic tolerance
Good HLA match
Technically successful surgery
Good graft function
Appropriate surgical prophylaxis
Effective antiviral prophylaxis
PCP prophylaxis
Appropriate vaccination

Small bowel transplantation (intestinal transplantation) is the treatment of choice in patients with intestinal failure and complications of parenteral nutrition. Many of the patients who undergo intestinal transplantation will have a heavily scarred abdominal wall from multiple abdominal procedures and previous bowel resections, which may cause technical difficulties during surgery and complications later on. Very often, small bowel and liver transplantation are combined when irreversible liver damage develops due to long-term parenteral nutrition. The small bowel is rich in lymphoid tissue, which increases the risk of allograft rejection. Patients undergoing small bowel transplantation have a higher incidence of infectious complications than other SOT recipients because of a very high load of microorganisms in the intestinal graft and because they require higher degrees of immunosuppression [7, 8]. Intra-abdominal abscesses also occur often as a consequence of bacterial translocation or peritoneal contamination during surgery [9].

2.2 Infection Risk and Classifications

Generally speaking, the risk of infection is determined by the intensity of the exposure to infectious agents (epidemiological exposures) and the net state of immunosuppression.

Epidemiological exposures can be divided into four overlapping categories: (1) donor-derived, (2) recipient-derived, (3) community, and (4) nosocomial exposures.

2.2.1 Donor-Derived Infections

This group comprises infections transmitted with donor organs generally in the form of latent infections (usually viruses such as cytomegalovirus – CMV), unrecognized colonization/infection of biliary or urinary tract, unknown bacteremia, or surgical contamination at procurement or preservation. Infected organ donors have been found to transmit bacteria and fungi carrying resistance to routine surgical antimicrobial prophylaxis [10, 11]. In addition, unexpected clusters of donor-derived infections in transplant recipients have been recognized including those due to West Nile virus, lymphocytic choriomeningitis virus (LCMV), rabies, HIV, hepatitis B and hepatitis C viruses, herpes simplex virus, tuberculosis, endemic fungi, and Chagas' disease [12, 13].

2.2.2 Recipient-Derived Infections

SOT recipients infected with latent or unrecognized pathogens before transplantation experience reactivation of such agents after surgery, generally during the period of maximum immunosuppression (1–6 months, see below). Common recipient-derived pathogens include viral infections (*Herpesviridae*, hepatitis B or C), *M. tuberculosis*, and in determined geographical areas endemic fungi (*Histoplasma capsulatum*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*) and some parasites (*Strongyloides stercoralis*, *Trypanosoma cruzi*). Traveling for tourism or other reasons, including medical purposes, has increased worldwide in the last few years, becoming a serious challenge for physicians who attend SOT recipients because unusual epidemiological exposures may result in atypical infection syndromes [14].

2.2.3 Community-Acquired Infections

Patients with favorable posttransplant clinical course and good graft function may present in the late period after transplantation (see below) with the common community-acquired infections as non-SOT recipients. The most common infections are respiratory (generally in the winter period triggered by a respiratory virus) [15] and urinary tract infections (most common in women and kidney transplant recipients). Atypical and severe manifestations are frequent in this setting. Furthermore, uncommon exposures related to employment, hobbies, travel, pets, or marijuana use (*Aspergillus* species) may determine unusual infection syndromes [16].

2.2.4 Hospital-Acquired Infections

These infections arise from surgical or perioperative complications. Thus the involved pathogens are typically those of nosocomial infections. Indeed, the major threat of such infections is represented by antimicrobial resistance.

2.2.5 Net State of Immunosuppression

The concept of the "net state of immunosuppression" comprises all factors that may contribute to risk for infection [16]. Preexisting disease processes have an important role. Renal failure and dialysis are associated with poor responses to bacterial infections and colonization with hospital-acquired flora. Cirrhosis and portal hypertension reduce acute inflammatory responses (specific antibody formation, chemotaxis) and predispose to bacterial and fungal infections [17]. Breaches in mucocutaneous integrity (e.g., vascular and urinary catheters) and fluid collections (hematoma, ascites, effusions) favor microbial seeding. These infectious hazards must be added to the effects of immunosuppressive therapy. Multiple mechanisms of tolerance (e.g., central vs. peripheral deletion or anergy) have been demonstrated in patients with induced or spontaneous immunologic graft tolerance. Some gaps in function (e.g., NK cells, antiviral immunity) persist for months to years [16].

2.2.6 Timing of Infection

The natural epidemiology of infections following SOT has been well characterized [18]. Most infectious complications occur during the first year after transplantation, which is traditionally divided into:

1. The first month posttransplantation (early): these infections are almost always hospital acquired, nosocomial bacteria and *Candida* spp. being the most common causative agents. However, unexplained early infectious syndromes (hepatitis, pneumonitis, encephalitis, rashes, leukopenia) may reflect donor-derived infection.
2. One to six months posttransplantation (intermediate): viral pathogens and graft rejections are responsible for the majority of febrile episodes in this period. However, depending on the antiviral prophylaxis strategy, CMV and other herpesvirus infections may emerge subsequently. Recipient-derived latent infections (e.g., tuberculosis, endemic fungi, *T. cruzi*) may reactivate in this period, as well as new exposures to opportunistic agents (e.g., *Nocardia* spp., *Rhodococcus equi*, tuberculosis, mold fungi, *Cryptococcus neoformans*, *Strongyloides*) may result in severe infections. In patients taking TMP–SMZ prophylaxis, some opportunistic infections such as *Pneumocystis* pneumonia (PCP), *Listeria monocytogenes*, *T. gondii*, and susceptible *Nocardia* species are prevented; however, they can emerge after prophylaxis discontinuation [19].
3. More than 6 months posttransplantation (late): beyond the sixth month after AOT, the level of immunosuppression in the majority of patients has been

reduced to minimal levels. As a result, patients are no longer at high risk for opportunistic infections. In a minority of patients, such as those with a "never-do-well" graft, the opportunistic infections that characteristically occur during months 1–6 may still occur. Late-onset CMV disease may also manifest during this period, especially in CMV D+/R- AOT recipients who had received a prolonged course (6 months) of antiviral prophylaxis [20].

The timeline is used to establish a differential diagnosis for infectious syndromes at various stages after transplantation. Infections occurring outside the usual period or of unusual severity suggest excessive immunosuppression or epidemiological hazard. The timeline is "reset" to the period of greatest risk for opportunistic infection with the treatment of graft rejection or intensification of immune suppression (e.g., bolus corticosteroids or T-cell depletion) [16]. Changes in immunosuppressive regimens, routine prophylaxis, and improved graft survival may also alter the timeline somewhat.

2.3 Major Etiologies and Their Management

The main infectious pathogens in AOT and their management are summarized in this paragraph.

2.3.1 Virus

2.3.1.1 CMV

CMV is a ubiquitous beta-herpesvirus that infects the majority of humans. The seroprevalence rates of CMV range from 30 to 97 % [21, 22]. In immunocompetent individuals, CMV infection manifests as an asymptomatic or self-limited febrile illness, after which CMV establishes lifelong latency in a small percentage of myeloid and dendritic cell progenitors, which serve as reservoirs for reactivation and as carriers of infection to susceptible individuals.

CMV is a major cause of morbidity and a preventable cause of mortality in solid organ transplant (SOT) recipients [23]. Without a prevention strategy, CMV disease typically occurs during the first 3 months after SOT; this onset has been delayed in SOT patients receiving CMV prophylaxis [24, 25].

In the SOT recipients, CMV may be responsible for primo-infection, reactivation, and/or disease.

1. CMV infection: infection usually occurs in a seronegative recipient who receives a graft from a seropositive donor (mismatch D+/R-). Seronegative recipients may also acquire CMV infection by blood transfusions. After a CMV primo-infection, the progression to severe disease is frequent in SOT recipients.
2. CMV reactivation: reactivation of CMV in seropositive recipients may occur during the intermediate period. Depending on the immunological host response, reactivation may progress to disease or clear spontaneously.

3. CMV disease: CMV infection or reactivation accompanied by clinical signs and symptoms. CMV disease is categorized into (1) CMV syndrome, which manifests as fever and/or malaise, leukopenia, or thrombocytopenia, and (2) tissue-invasive CMV disease (e.g., gastrointestinal disease, hepatitis, nephritis, pancreatitis). CMV has a predilection to invade the allograft, likely in part due to an aberrant immune response within the allograft.

CMV also has numerous indirect effects due to its ability to modulate the immune system. CMV has been associated with other infections such as bacteremia, invasive fungal disease, and Epstein–Barr virus-associated posttransplant lymphoproliferative disease [26]. CMV infection is an important contributor to acute and chronic allograft injury, including chronic allograft nephropathy or tubulointerstitial fibrosis in kidney recipients and chronic biliary stenosis in liver recipients [27].

CMV replication may be detected [23] by nucleic acid testing, antigen testing, and/or culture. Depending on the method used, CMV infection can be termed as CMV DNAemia or RNAemia, CMV antigenemia, and CMV viremia. Given their greater sensitivity, rapidity of response, and ease of execution than the other tests, molecular methods are currently the most used techniques for detection of CMV replication. However, there is still heterogeneity in the types of molecular methods used, which are generally homemade polymerase chain reaction tests detecting CMV DNA or RNA, the type of analyzed specimen (plasma or whole blood), and the way to report the quantitative amount of viral replication (UI/ml or copies/ml). The lack of an international reference standard and variation in assay design [23] have prevented the establishment of broadly applicable cutoffs for clinical decision-making, particularly for preemptive strategies.

As stated above, a major risk factor for CMV disease after SOT is primo-infection. In CMV D+/R- patients, given the absence or weakness of specific T-cell immunological response, viral replication is intense, producing the abovementioned direct and indirect effects.

Prevention of CMV disease is based on two types of strategies: universal prophylaxis (administration of antiviral therapy to all patients at risk) and preemptive therapy (weekly screening for CMV replication and initiation of an antiviral treatment in case of a preestablished level of CMV DNAemia) [28]. A recent comprehensive meta-analysis failed to show the presumptive superiority of universal prophylaxis, in terms of protection by direct and indirect CMV effects, over preemptive strategy [29]. However, current guidelines recommend universal prophylaxis in CMV D+/R- and R+ recipients, during 3–6 months in liver and kidney recipients, and for a minimum of 6 months in patients undergoing intestinal transplantation [23]. Oral valganciclovir at the dosage of 900 mg/day is currently the most used agent for this scope given its efficacy, feasibility, and lower rate of adverse events compared with ganciclovir. There are limited data to support the use of CMV immunoglobulin (CMV Ig) for prophylaxis when appropriate antivirals are given. Some centers use these products in conjunction with antiviral prophylaxis, primarily for high-risk thoracic and intestinal transplant recipients.

The main disadvantages of universal prophylaxis are (i) the occurrence of late CMV infection which seems to be associated with a higher rate of severe disease

and (ii) high exposure to antiviral agents with a substantial risk of resistance selection [23]. Evidence exists in support of a hybrid approach, initial universal prophylaxis followed by preemptive therapy [29]. The major disadvantage of preemptive therapy is the need for weekly testing for CMV DNAemia. However, recent studies suggest that the determination of CMV viremia may be done less frequently if the patient has recovered the CMV-specific T-cell response [30, 31]. Recent guidelines also suggest the use of some of the currently available techniques to determine the CMV-specific T-cell response in order to tailor the CMV preventive strategy to the specific patient risk [23].

Therapy for CMV disease in this population does not differ from other SOT patients. Intravenous ganciclovir (5 mg/Kg every 12 h) is preferred as initial treatment, mainly in severe disease, followed by oral valganciclovir (900 mg every 12 h). Some experts prefer to prolong therapy with valganciclovir at prophylaxis dosage for another 2 weeks after symptom resolution and clearance of viremia.

2.3.1.2 EBV

The incidence of posttransplantation lymphoproliferative disease (PTLD) related to Epstein–Barr virus (EBV) is highest in intestinal recipients in which it is up to 32 %, varying between 3–12 % in liver transplant recipients and 1–2 % in kidney recipients [32]. Recently, Caillard also described a temporal sequence of sites of PTLD involvement in adult renal allograft recipients, with disease localized to the graft occurring within the first 2 years, CNS disease occurring between years 2 and 7, and gastrointestinal disease occurring between years 6 and 10 and becoming the predominant site of late disease [33]. Although PTLD in SOT recipients is most often of recipient origin [34], PTLD limited to the graft and occurring early after transplant is predominantly donor in origin [35].

More than half of patients are symptomatic, presenting with a mononucleosis-like picture with lymph node swelling, isolated PTLD lesions in the gastrointestinal tract, disseminated disease, or lymphoma. Risk factors for PTLD are primary infection and therapy with OKT3 or antithymocyte globulins. When PTLD is suspected, CT of the neck, chest, abdomen, and pelvis should be considered to identify occult lesions. Biopsies should be obtained from suspicious lesions. Patients with active EBV disease typically have an elevated EBV viral load, which may be detected before clinical onset and may remain persistently high even after resolution of PTLD.

The high rates of morbidity and mortality attributed to PTLD have prompted efforts aimed at the prevention of EBV [32]. Serial monitoring of the EBV viral load using quantitative PCR assays has been shown to predict occurrence of PTLD in transplant populations and is increasingly being used to guide initiation of preemptive therapy. However, specific target levels of load and specific sites to sample (blood versus tissues), as well as therapeutic preemptive treatment regimens, need to be clarified. The management of patients with PTLD is controversial. Reduction of immune suppression is uniformly recommended in order to enhance a cytotoxic T lymphocyte response. Concerns over the development of rejection can limit this approach. While frequently used, antiviral therapies (primarily nucleoside

analogues – e.g., ganciclovir – and immunoglobulins) are probably of limited benefit for the treatment of EBV PTLD. The use of anti-CD20 monoclonal antibody (rituximab) may be necessary for patients who fail to respond to reduction of immunosuppression or in whom the PTLD lesions are judged to be malignant [32].

2.3.1.3 Other *Herpesviridae*

Among *Herpesviridae*, herpes simplex virus (HSV) and varicella-zoster virus (VZV) may reactivate or cause primary infection with a more aggressive course including hemorrhagic and visceral lesions than in non-SOT recipients. Some experts recommend acyclovir prophylaxis for seronegative patients or those who experienced several reactivations before transplantation [36].

VZV infection should be prevented in seronegative patients who have contact with individuals with varicella or herpes zoster by the administration of hyperimmune globulin. VZV vaccine should be given to seronegative patients before transplantation.

HHV-8 is associated with Kaposi's sarcoma (KS), Castleman's disease, primary effusion lymphoma, and a nonmalignant but highly fatal disease characterized by fever, hemophagocytosis, myelosuppression, and multiorgan failure. In one study, the incidence of Kaposi's sarcoma (KS) was 0.28 % after kidney transplantation. KS was diagnosed a median of 24 months after SOT, and mortality was 28.5 %. Primary infection with human HHV-8 was found to be an important risk factor.

2.3.1.4 BKV

The human BK polyomavirus (BKV) is linked to two major complications in transplant recipients, polyomavirus-associated nephropathy (PyVAN) in 1–10 % of kidney transplant patients and polyomavirus-associated hemorrhagic cystitis (PyVHC) in 5–15 % of allogeneic hematopoietic stem cell transplant (HSCT) patients. Both diseases occur only sporadically in patients with non-kidney SOT or with inherited, acquired, or drug-induced immunodeficiency.

Primary infection with BKV occurs in the first decade of life as evidenced by increases in BKV seroprevalence to 90 % and more. Natural BKV transmission is not understood, but likely occurs via the respiratory or oral route. Subsequently, BKV colonizes the reno-urinary tract as the principle site of latent infection, most likely via a primary viremia. In healthy BKV seropositive immunocompetent individuals, reactivation and asymptomatic urinary shedding of BKV is detectable in up to 10 %. In individuals with impaired immune functions, particularly after SOT or HSCT, asymptomatic high-level urinary BKV replication is observed with high-level BKV viruria and appearance of "decoy cells" in urine cytology. High-level BKV viruria only rarely leads to viremia and PyVAN in non-kidney SOT. In kidney transplant recipients, however, approximately one-third of patients with high-level viruria/decoy cells develop BKV viremia and, in the absence of any intervention, progress to histologically proven PyVAN. This progressively affects graft function and increases the risk of graft loss from <10 % to more than 90 %.

Because effective and safe antiviral therapies are lacking, screening for BKV replication has become the key recommendation to initiate and guide a stepwise

reduction of immunosuppression. This intervention allows for expanding BKV-specific cellular immune responses, curtailing of BKV replication in the graft, and clearance of BKV viremia.

In KT recipients, current guidelines [37] recommend screening for BKV replication at least every 3 months during the first 2 years posttransplant and then annually until the fifth year posttransplant. Screening for BKV replication can be done either by testing urine for high-level BKV viruria/decoy cells or by testing plasma for BKV viremia. Monthly plasma screening is preferred in many centers as it detects clinically more significant replication and provides a widely accepted trigger for therapeutic intervention. Detecting BKV viremia can guide more specific histopathology studies. The definitive diagnosis of PyVAN should be sought by demonstrating PyV cytopathic changes in allograft tissue and confirmed by immunohistochemistry or in situ hybridization ("proven PyVAN").

Reducing immunosuppression should be considered for KT patients with sustained plasma BKV loads and is mandatory in KT patients with proven PyVAN. In patients with sustained high-level plasma BKV load despite adequately reduced immunosuppression, the adjunctive use of antiviral agents may be considered. The proposed options include cidofovir, leflunomide, fluoroquinolones, and IV IgG. However, there are no robust data regarding the benefit of these agents. Retransplantation can be considered for patients after loss of a first kidney allograft due to PyVAN, but frequent screening for BKV replication is recommended.

2.3.2 Bacteria

Bacterial infections, especially those involving Gram-negative bacteria, represent a major complication in AOT, the frequency ranging between 20 and 80 % of recipients, and they contribute to longer hospital stays and increased hospital costs [38]. Three-fourths of bacterial infection episodes occur in the first month after transplantation. In LT recipients, intra-abdominal (including the biliary tree) and surgical site infections are the most common types of infections, followed by lower respiratory tract infections, catheter-related bloodstream infections, and urinary tract infections [39]. After KT, surgical site infections and urinary tract infections are the leading bacterial infections [40].

Perioperative antibiotic prophylaxis has been shown to be effective in reducing the rate of surgical site infections after SOT [41]. Any transplant program should establish drug, timing, and duration of perioperative prophylaxis on the basis of local epidemiology and type of surgery (duration, complications, etc.). In the case of infection with an MDR pathogen in the donor, the antibiotics used in prophylaxis should be active against the isolated pathogen, and therapy may be prolonged 7–14 days after transplantation depending on the type of infection [13, 42]. The use of wide-spectrum antibiotic prophylaxis also for recipients colonized with an MDR pathogen should be carefully considered for potential toxicity and emergence of further resistance [43]. In LT recipients, some experts have proposed the use of selective intestinal decontamination (SID) with antibiotics, but its efficacy and

safety in the prevention of bacterial infections are still a matter of debate. A recent study from Spain did not confirm that fluoroquinolones administered from the time of transplantation have any protective effect against development of early bacterial infections after LT [44]. On the other hand, most pathogens recovered from infected LT recipients undergoing SID were resistant to quinolones [44].

2.3.2.1 MDR Pathogens

Given the frequent exposure to antibiotics for treatment and prevention purposes, the high rate of invasive procedures, the use of indwelling devices, and the prolonged hospitalization, patients undergoing AOT are at very high risk for acquiring infection due to MDR bacteria. Studies performed a decade ago reported Gram-positive bacteria as a leading cause of bacterial diseases in SOT recipients with a high rate of methicillin-resistant *Staphylococcus aureus* (MRSA) [38]. However, Gram-negative bacteria have recently overcome Gram-positive bacteria with *Enterobacteriaceae* being the leading pathogens, mainly in the AOT setting. Along with the reemergence of Gram-negative bacteria in this setting, carbapenem-resistant *Enterobacteriaceae* (CRE) has spread worldwide over the last decade, becoming a serious healthcare problem [45].

Among CRE, the most common pathogen is carbapenem-resistant *Klebsiella pneumoniae* (CR-KP). SOT has been shown to be an independent risk factor for CR-KP infection [46]. The emergence of CR-KP has been best evaluated in LT recipients for whom the incidence of CR-KP infection after transplant, in endemic areas, is approximately 5 %. Infection mainly occurs early after LT, although some authors have also reported a late occurrence with 50 % of episodes observed after the first month from transplant [47]. The abdomen is frequently the portal of entry of CR-KP infections in this setting with a high rate of bloodstream involvement (>80 %) [45]. The overall mortality of LT recipients infected with CR-KP varies between 25 and 78 % [47, 48].

Given the worse outcome and the limited therapeutic options, prevention of CR-KP in the AOT setting is of paramount importance. To prevent the spread of CR-KP in healthcare facilities, a number of recommendations have been made, including optimizing compliance with hand hygiene and contact precautions, educating healthcare personnel, minimizing the use of indwelling devices, implementing antimicrobial stewardship programs, and active screening for CR-KP colonization [49]. However, currently there is no agreement for the universal screening of asymptomatic LT candidates and recipients, as there are no data regarding the benefit of this screening [50]. Furthermore, there is no agreement for the management of colonized patients, as there are no data about the efficacy of the proposed approaches such as deferring LT, selective intestinal decontamination, antibiotic prophylaxis active against CR-KP, and/or empirical anti-CR-KP therapy. On the other hand there is concern for toxicity and emergence of further antibiotic resistance as a consequence of an overuse of antibiotics active against CR-KP [51].

At our center we have recently prospectively analyzed the impact of colonization before and after LT and other variables on CR-KP infection development in all patients undergoing LT from June 2010 to December 2013. Of the 237 patients who

underwent LT, 196 were non-CR-KP carriers, 11 were CR-KP carriers at LT, and 30 patients acquired colonization within a median of 14 days after LT. The CRE infection rates in these three groups were 2, 18.2, and 46.7 % ($p<0.001$), respectively. Four variables were independently associated with infection: need for renal replacement therapy, prolonged mechanical ventilation >48 h, histological evidence of hepatitis C recurrence, and CR-KP colonization [52]. In our study, CR-KP colonization acquired after LT predisposed to a higher risk for CR-KP infection than colonization at LT, and thus we believe that in endemic areas active screening for CR-KP colonization should be performed not only before but also after LT. Empirical therapy active against CR-KP may be indicated only for symptomatic colonized patients with a complicated post-LT clinical course.

In a recent single-center retrospective case-control study of 13 KT recipients who developed CR-KP infection during 2006–2010, CR-KP infections were significantly associated with recent exposure to broad-spectrum antibiotics and were more likely to have been managed on an inpatient basis and to have required source control. CR-KP was significantly associated with earlier mortality. Six of 13 (46 %) patients with CR-KP infection and none of the controls died within 6.5 months of infection onset [53]. The authors concluded that investigations on ways to better prevent CR-KP are urgently needed.

Studies on the general population of patients with CR-KP infection have shown that source control and prompt initiation of adequate therapy are associated with better survival [54, 55]. Available clinical data on the treatment of CR-KP infection have demonstrated that (1) monotherapy is associated with lower success rates than combination therapy and increased risk of resistance to "second-line" antibiotics, i.e., colistin, tigecycline, and fosfomycin, and (2) carbapenem-containing combinations are more effective than non-carbapenem-containing regimens, especially for isolates with MICs <4 mg/L. Currently, the MIC "ceiling" precluding the beneficial use of carbapenems is unknown, but a benefit has been observed in case series against isolates with MICs up to 16 mg/L. The selection of specific second-line agents should be individualized to the local resistance patterns, site of infection, and specific toxicity risks of the patient. Antibiotic loading doses should be considered for any patient with suspected CR-KP infection, especially if the patient is critically ill and has evidence of impending or florid sepsis. Contemporary pharmacokinetic studies of carbapenems, colistin, and tigecycline have utilized loading doses to optimize drug activity and exposures early in the course of treatment.

2.3.2.2 *Clostridium difficile*

C. difficile is an anaerobic, Gram-positive, spore-forming bacillus. *C. difficile* causes inflammatory diarrhea via two exotoxins, toxin A and toxin B, which trigger a cytotoxic response, neutrophilic infiltrate, and cytokine release [56]. The incidence of CDI is estimated to be 3–19 % in liver recipients, 3.5–16 % in kidney recipients, 1.5–7.8 % in pancreas–kidney recipients, and 9 % in intestinal recipients [57]. The incidence of *C. difficile* infection (CDI) in SOT recipients is highest within the first 3 months after the procedure, probably because of more frequent antimicrobial exposure, intense immunosuppression, and increased exposure to the healthcare

setting. Late-onset CDI occurs months to years after the transplant and is usually associated with either antimicrobial exposure or intensified immunosuppression to treat graft rejection. In a recent retrospective cohort study of all kidney and liver transplant recipients diagnosed with CDI at a single center over 14 years, 170 patients developed 215 episodes of CDI [58]. Among these patients, 162 episodes (75 %) were cured, 13 patients (8 %) died during hospitalization, and 49 patients (29 %) died within 1 year. No deaths were attributed to CDI. Recurrent episode was a major predictor of treatment failure [58].

The laboratory gold standard for *C. difficile* toxin detection in stool is the cytotoxicity cell assay, and the gold standard for detecting toxin-producing *C. difficile* is toxigenic culture. However, cytotoxicity cell assays have fallen out of favor because they are relatively labor intensive and involve a delay of at least 24 h before interpretation [56, 59]. Currently, more hospitals are converting to a two-step algorithm that utilizes new molecular methods. Screening stool for the presence of glutamate dehydrogenase (GDH), a common cell wall protein produced by both toxigenic and nontoxigenic *C. difficile*, is the foundation for many of the new protocols. Testing for the presence of GDH allows rapid and cost-effective screening; however, as GDH does not differentiate toxigenic strains from nontoxigenic strains, subsequent toxin testing (by ELISA or NAAT) is required for those stool specimens that are GDH positive.

Severity of CDI can be divided into three categories: mild to moderate, severe, and severe with complications [60]. Of note, there are no validated methods to objectively categorize patients as such. Mild-to-moderate CDI symptoms are typically diarrhea and possibly also mild abdominal pain and abdominal systemic symptoms. Severe CDI includes abdominal pain, leukocytosis, and fever or other systemic symptoms along with profuse diarrhea. Advanced age and patients with hypoalbuminemia are at increased risk for severe disease. Severe disease with complications includes the symptoms of severe disease accompanied by life-threatening conditions such as paralytic ileus, toxic megacolon, refractory hypotension, and/or multiorgan failure secondary to CDI. The disease severity may rapidly progress, so clinicians should frequently reassess and adjust therapy accordingly.

The first intervention that should occur in any patient with CDI is cessation of the inciting antimicrobial agent whenever possible. Published guidelines support basing the initial antibiotic choice on the severity of CDI [57, 60]. Oral metronidazole (500 mg TID) is recommended for mild-to-moderate disease in both the general population and SOT recipients. However, a major disadvantage of metronidazole use in SOT recipients is an interaction with medications such as tacrolimus or sirolimus, so that levels should be monitored during treatment. Oral vancomycin (125 mg QID) is the preferred therapy for severe CDI. Several studies demonstrated improved response rates with vancomycin compared to metronidazole in severe disease. In contrast to metronidazole, vancomycin does not reach adequate levels in the feces when given intravenously and should never be administered intravenously to treat CDI. In 2011, fidaxomicin was FDA approved for the treatment of CDI. Fidaxomicin is a macrocycline (in the United States it is designated as a macrolide; in Europe as a macrocycle) antibiotic with minimal systemic absorption,

high colonic concentrations, and limited impact on normal gut flora. It has been evaluated in patients with no or one prior episode of CDI. Data reveal similar clinical response, but decreased rates of recurrent infection, as compared with vancomycin 125 mg orally every 6 h [61]. Limitations to fidaxomicin include drug acquisition costs and lack of data in SOT recipients. In cases of severe CDI with complications, decreased gastrointestinal motility may limit the efficacy of oral vancomycin by preventing the drug from reaching the site of infection. In these patients, 500 mg every 6 h of oral vancomycin may be warranted in an attempt to increase the probability that adequate levels of vancomycin will be achieved in the colon as quickly as possible. Several case reports also support the use of vancomycin administered by retention enema in cases of ileus [57]. Surgical intervention within the first 48 h of a failure to respond to medical therapy, bowel perforation, or multiorgan failure may reduce mortality in patients with severe disease [57]. Serum lactate levels and peripheral WBC count may be helpful in determining timing of surgical intervention. Lactate levels rising to 5 mmol/L and WBC count rising to 50,000 cells/lL are associated with perioperative mortality; thus, intervention prior to reaching these cutoffs should be considered.

Twenty to 30 % of patients with CDI will suffer at least one recurrence [56]. Patients treated with fidaxomicin have demonstrated fewer episodes of recurrent CDI, though studies to date have not included transplant recipients. Treatment of the first recurrence should again be guided by the disease severity as recurrence is not related to the development of antimicrobial resistance to the first course of treatment [56]. Management of patients with multiple recurrences has not been thoroughly studied, but there are reports of success with either a prolonged tapering or pulse-dosing schedule of oral vancomycin.

Fecal microbiota transplantation (FMT) has been shown to be safe and efficacious in individuals with refractory CDI [62]. It has not been widely studied in individuals with immunosuppression due to concerns about infectious complications. Case reports and surveys on immunocompromised hosts, including SOT recipients, undergoing FMT due to refractory CDI have been reported with a high rate of success (approximately 80 %) and low incidence of severe adverse events.

2.3.3 Mycobacteria

SOT recipients are at increased risk of mycobacterial infections. Classically mycobacterial diseases can be divided in *Mycobacterium tuberculosis* infection and non-tuberculous mycobacterial infection.

2.3.3.1 Tuberculosis

Mycobacterium tuberculosis infection (TB) is a serious complication of AOT. SOT candidates and recipients are at greater risk for developing active TB with a rate of occurrence up to 74 times higher than that of the general population. The incidence rate of TB in SOT recipients can show a wide variability between (1) endemic (15 % of cases) and non-endemic countries (0–6 % of cases), (2) type and intensity of

immunosuppression, and (3) transplantation setting, being more frequent in lung recipients than other SOT. Most cases occur within 6 months from transplantation with the exception of renal transplantation where the median time of onset is 11.5 months after transplantation [63].

TB in SOT patients can have peculiar clinical features, such as a more frequent involvement of extrapulmonary organs and atypical symptom and signs leading to a delayed diagnosis and, consequently, to a worse outcome. Thus, TB-related mortality may reach 30 % in the SOT setting.

In SOT recipients, TB may be represented by four different scenarios, some of which can be prevented with a specific strategy [64]:

(a) *Endogenous reactivation due to latent infection with M. tuberculosis* (*LTBI*) *in the candidate recipient*. This is the most common pattern of TB infection. Candidates to SOT should be evaluated and screened for LTBI with a careful evaluation of patient history, including previous exposure to *M. tuberculosis* (MTB), and sign/symptoms. Methods measuring immune response to MBT are widely accepted to detect LTBI. These include tuberculin skin tests (TSTs) and INF-γ release assays (IGRAs). When compared to TST, IGRAs have some operational advantages that are particularly relevant in immunocompromised patients. Unlike the TST, antigen-specific stimulation in vitro is carried out along with negative and positive controls. As the positive control allows assessment of general T-cell responsiveness, IGRA tests may be able to discriminate true negative responses from anergy and/or overt immunosuppression. Further advantages of IGRAs may result from an increase in specificity in the face of increased, or at least similar, sensitivity. SOT candidates in which an LTBI is diagnosed have to be treated with a 9-month course of isoniazid, unless they have already received adequate treatment for LTBI or TB. In certain circumstances in AOT patients (i.e., LT candidates with end-stage liver disease), isoniazid treatment can be deferred to the postsurgical period for the increased risk of drug-induced hepatotoxicity.

(b) *Donor-derived reactivation due to LTBI in a living or deceased donor* is rare in AOT, while it is predominant in lung transplantation. However, cases of TB transmission with LT and KT with high fatality rate have been reported. Donors, similarly to recipients, should be evaluated and screened for active or LTBI. A suspicion of active TB should be contraindicated for donation.

(c) *De novo exposure and infection posttransplantation*. In SOT patients the risk of rapid progression of TB is high in the case of a de novo infection with a frequent extrapulmonary involvement and/or disseminated infection.

(d) *Urgent transplantation in a patient with active tuberculosis* (i.e., *urgent liver transplantation*). Even though TB is considered a contraindication for organ transplantation, in specific cases of fulminant hepatic failure (FHF), LT has been successfully performed. We recently reviewed the literature and found 31 cases of LT reported in patients with active tuberculosis. The indication for LT was fulminant hepatic failure (FHF) in 22/31 (70 %) of cases, secondary to antitubercular treatment (ATT), hepatitis B virus, or idiopathic in 86, 9, and 4 %

of cases, respectively. At the end of follow-up which lasted a median of 12 (12–24) months, 27/31 (87 %) patients were alive, and none of them experienced a relapse of TB after LT.

Treatment of TB after SOT remains a challenge [64]. First-line ATT including isoniazid, rifampin, pyrazinamide, and ethambutol is recommended in susceptible strains. However, the potential for drug interaction between rifaximins and immunosuppressant agents and hepatotoxicity of antitubercular drugs make strict monitoring of immunosuppressant serum levels and liver function tests mandatory while administering rifampin and isoniazid, especially after LT. In this latter setting, in fact, hepatotoxicity requiring isoniazid discontinuation was documented in 41 % of recipients. Adequate immunosuppressant drug serum levels can be easier to maintain with the use of rifabutin instead of rifampin, for the lesser potential of cytochrome P3A4 induction of rifabutin. Second-line drugs such as fluoroquinolones and aminoglycosides have been successfully used and are preferred by some authors for the absence of potential hepatotoxicity and low risk of drug interaction. A rifamycin-free regimen (H, Z, E, fluoroquinolone) is an option in non-severe TB cases (non-cavitated pulmonary and nondisseminated disease) in order to avoid interaction with immunosuppressive drugs.

2.3.3.2 Nontuberculous Mycobacteria

Nontuberculous mycobacteria (NTM) infections are rare in SOT patients if compared with other posttransplant infections [65]. However, their importance is due to challenges in diagnosis and treatment. NTM include a broad spectrum of pathogens and consequently comprise a wide range of diseases and clinical manifestations. The most common infections are caused by *Mycobacterium avium–intracellulare complex* (MAC), *M. xenopi*, *M. kansasii*, *M. marinum*, *M. haemophilum*, and the rapid growing mycobacteria (RGM): *M. fortuitum*, *M. chelonae*, and *M. abscessus*. The main clinical features of NTM include lung disease, skin and soft tissue infection, and lymphangitic eruption. Nearly half the infections initially confined to the lung can evolve rapidly into a disseminated disease that can involve the lungs, nodes, visceral organs, and bone marrow. Table 2.2 summarizes the main clinical manifestation and treatment of NTM in SOT patients.

2.3.4 Fungi

Invasive fungal infection (IFI) is a main cause of morbidity and mortality among SOT recipients [66]. Incidence and sort of IFI typically show strict dependence on the kind of organ transplanted and the intensity of immunosuppression, consequently varying from center to center [67, 68]. Among AOT, due to the complexity of intraperitoneal surgical procedures, invasive candidiasis (IC) is the most common IFI, accounting for 49–76 % of cases, followed by invasive aspergillosis (IA) (5–14 %) and zygomycoses (0–2 %) [67, 68]. IC is prevalent especially in the first posttransplant period where the risk of surgical complication, antibiotic exposure,

Table 2.2 Main clinical manifestation and treatment of NTM in SOT patients

Clinical presentation	Causing pathogen	First-line treatment	Second-line treatment	Length of treatment
Lung disease	*M. avium complex*	Azithromycin/clarithromycin Rifabutin Ethambutol	Rifampin Amikacin or streptomycin	12 months after negative cultures
	M. kansasii	Rifadin Ethambutol Isoniazid[#]	Rifampin Azithromycin/clarithromycin Amikacin or streptomycin Sulfamethoxazole Moxifloxacin	8 months with at least 12 months of negative cultures
	M. xenopi	Azithromycin/clarithromycin Rifabutin Ethambutol		
	M. abscessus	Azithromycin plus either amikacin, imipenem, or cefoxitin	Clarithromycin Linezolid	
Skin and soft tissue infection (includes ulcers, subcutaneous nodules, surgical wound infection)[*]	*M. fortuitum*	Amikacin Ciprofloxacin	Sulfonamides Tetracyclines Imipenem Tigecycline	
	M. abscessus	See before	See before	
	M. chelonae	Azithromycin plus either linezolid, tigecycline, or imipenem	Susceptibility test	
Lymphangitic eruption	*M. marinum*	Azithromycin/clarithromycin Ethambutol ± rifabutin	Rifampin Amikacin or streptomycin Sulfonamides Tetracyclines	3–4 months with at least 2 months after symptoms resolve
Disseminated disease	*MAC*	See before	See before	
	M. kansasii			
	M. chelonae			
	M. abscessus			

[#]Add pyrodoxin

[*]Surgical drainage of abscesses or resection of necrotic/infected tissue should be encouraged

and immunosuppression is highest. The median time to onset is usually 103 days after transplantation for IC and 184–234 days for IA [67, 68]. Depending on the kind of transplantation, the incidence of IFI is more frequent in small bowel transplantation, followed by liver transplantation, and is lowest among kidney recipients.

Common risk factors for IC in SOT are acute renal failure, recent CMV infection, primary graft failure, transfusion of ≥40 units of cellular blood products, and early colonization with *Candida* spp. [69]. In addition, each transplantation setting can have specific risk factors such as choledochojejunostomy in LT or enteric drainage in pancreas transplantation. Risk factors for IA are well established, especially among LT recipients, and include retransplantation, urgent transplantation for fulminant hepatic failure, renal failure requiring renal replacement therapy, and relaparotomy [70].

Diagnosis of IFI in SOT patients is challenging [71]. Prompt recognition of fungal infection is essential for achieving a successful outcome. However, sensitivity of blood cultures for the diagnosis of IC is low (almost 50 %), and the performance of non-culture methods such as beta-D-glucan in this setting has been rarely investigated. For IA, both clinical symptoms and radiologic manifestations may be nonspecific at early stages of the disease. The isolation of *Aspergillus* spp. from non-sterile respiratory samples may indicate invasive infection, colonization, or laboratory contamination, thus making treatment of asymptomatic transplant recipients difficult. However, the isolation of *A. fumigatus* is highly predictive of invasive disease and should always be considered very seriously in this population. All respiratory samples other than sputum proved to have the same predictive value; thus, the choice of one or another technique should be based on the availability and expertise in each hospital, on the extent and location of the infiltrate, and on patient characteristics. Previous studies have shown that in SOT recipients with pneumonia, the sensitivity of bronchoalveolar lavage for IA diagnosis ranged from 58 to 89 %, and transthoracic aspiration reached 100 % sensitivity. Clinical and microbiologic information should be combined with early CT scan, which provides more specific information than conventional chest X-ray. Although detection of galactomannan in serum has poor sensitivity for the diagnosis of invasive aspergillosis in LT recipients, detection of galactomannan in the bronchoalveolar lavage with a compatible clinical illness is highly suggestive of invasive disease [70]. Central nervous system (CNS) involvement in this setting is common; thus, CT scan of CNS and paranasal sinuses is strongly recommended in SOT patients with IA diagnosis to rule out extrapulmonary disease.

Antifungal prophylaxis is recognized as a useful strategy to reduce the incidence IFI and the IFI-related mortality after LT [72]. Prophylaxis with newer oral triazoles is limited by wide intra- and interindividual pharmacokinetic variability resulting in unpredictable blood levels, as well as numerous interactions with immunosuppressive agents. The use of echinocandins in solid organ transplant recipients has been shown to be safe with a low rate of drug–drug interactions. However, the need for daily parenteral administration and increasing reports of breakthrough infections have dampened enthusiasm for use of these agents [73]. In a recent phase II trial, a weekly high dose (10 mg/kg) of liposomal

amphotericin B (LamB) was reported to be safe, feasible, and associated with a very low rate of IFI [74].

Prompt initiation of antifungal treatment is necessary in cases of IFI. Echinocandins are the antifungal of choice for IC especially in critically ill patients and in settings with a high rate of fluconazole resistance. However, treatment with echinocandins in AOT may fail to penetrate the tissues in cases of intra-abdominal infection such as *Candida* peritonitis [75]. In this case, LamB may be a potential alternative. Fluconazole remains the preferred treatment in patients with stable condition or after clinical stabilization as a step-down therapy.

For many authors, voriconazole is the drug of choice in cases of IA in SOT, especially in cases of extrapulmonary spread of infection. In a randomized trial, voriconazole showed superiority in the treatment of IA compared with amphotericin B deoxycholate. During the treatment with voriconazole, serum levels of immunosuppressant agents and the triazole should be carefully monitored for important drug-to-drug interactions. Liposomal amphotericin B (LamB) is a good alternative to voriconazole. LamB has a broad-spectrum antifungal activity, is generally well tolerated, and has little or no interactions with antirejection drugs. Combination treatment with azoles and echinocandins is a promising option as a rescue therapy for IA, although data on its overall benefit are still controversial [76].

2.4 Prevention

Antimicrobial prophylaxis has significantly altered the incidence and severity of posttransplant infections. Indeed, prevention of invasive disease, whether resulting from new exposure or from the activation of existing latent infection, is easier than the treatment of established disease [16]. *Six general preventive strategies are used*: (*1*) *vaccination*, (*2*) *surgical prophylaxis*, (*3*) *universal prophylaxis*, (*4*) *preemptive or presymptomatic therapy*, (*5*) "*targeted prophylaxis*," *and* (*6*) *educated avoidance*.

Pre-transplant recipient and donor assessment is critical to assess the patient risk and schedule prophylactic strategies (see Tables 2.3 and 2.4). In the pre-transplant period, it is also important to update the vaccination status to guarantee a higher efficacy of these strategies (see Table 2.5) [77].

As mentioned above, routine surgical prophylaxis should be adjusted to the organ transplanted and hospital epidemiology. Some authors suggest that surgical prophylaxis may be adjusted based on known colonization patterns with organisms such as *Pseudomonas*, MRSA, VRE, KPC, or fungi, but there are no data about the efficacy of this strategy, while there is considerable concern regarding toxicity and selection of further resistance.

"Educated avoidance" includes lifestyle changes that may limit exposure to potential pathogens (wearing masks or gloves while gardening, avoiding attics or basements with molds, filtered water supplies).

Two advances in prophylaxis have significantly altered transplant medicine. First, trimethoprim–sulfamethoxazole (TMP–SMZ) is given at most centers for

Table 2.3 Donor and recipient pre-SOT assessment for prevention of viral infections

	D	If test is positive	R	If test is positive
Ab HIV 1/2	×	Contraindicated but considered for HIV+ recipient	×	Not contraindicated in pts with:
				1. No detectable viral replication
				2. CD4+ > 200/μL
				3. Therapeutic reserve
IgG CMV	×	Not contraindicated but essential to define prophylactic strategy	×	
IgG EBV	×	Not contraindicated but essential to monitor EBV-negative recipients, especially children	×	
Ab HHV8	×	Not contraindicated but essential to monitor HHV8-negative recipients	×	
HBsAg	×	Contraindicated but considered for HBsAg + or HBV-immunized pts	×	
HBcAb	×	Not contraindicated, but consider antiviral prophylaxis for liver and HBV nonimmune recipients	×	
Ab HCV	×	Contraindicated but considered for HCV+ recipients	×	

Table 2.4 Donor and recipient pre-SOT assessment for prevention of bacterial infections

	D	If test is positive	R	If test is positive
TPHA, VDRL	×	Not contraindicated, but treat the recipient	×	Not contraindicated, but treat the recipient
Blood cultures	×	Not contraindicated, but treat the recipient. Individual decision in case of MDR bacteria		
Bronchoscopy with BAL	×	Mandatory for lung donor and recipient. Individual evaluation in case of MDR, fungal, and mycobacterial colonization		
Surveillance cultures		Culture of preservation fluid is highly controversial	×	There is no agreement about management of patients colonized with MDR bacteria
PPD/IGRA		Deceased donor evaluation for TB relies on medical history, endemic exposures, and Rx findings	x	Exclude active TB. Latent and active TB should be treated before SOT (if possible)

3 months to lifetime to prevent *Pneumocystis* pneumonia (PCP) as well as *Toxoplasma gondii*, *Isospora belli*, *Cyclospora cayetanensis*, many *Nocardia* and *Listeria* species, and common urinary, respiratory, and gastrointestinal pathogens. Low-dose TMP-SMZ is well tolerated and should be used in the absence of specific data demonstrating allergy or interstitial nephritis. Alternative anti-*Pneumocystis* prophylactic strategies lack this breadth of protection [77].

Table 2.5 Vaccination in SOT candidates and recipients

	Scheme	Before Tx	After Tx	Booster
Varicella	2 doses (0, 1 month)	Last dose 1 month before Tx	Contraindicated	–
MMR	2 doses (0, 1 month)	Last dose 1 month before Tx	Contraindicated	–
S. pneumoniae	1 dose	Last dose 2 weeks before Tx	After 6 months of Tx	Once after 5 years
Influenza	1 dose			Every year
HBV	0, 1, 2, 12 months Double dose if high immunosuppression			If anti-HBs <10 mU/ml
HAV	2 doses (0, 6 months)			Once in nonresponders
dT	According to previous immunization status			Every 10 years (dT or dTpa)

The prevention of posttransplant cytomegalovirus and other herpesvirus infections, including the availability of some oral antiviral agents and the use of nucleic acid-based assays to establish a specific microbiologic diagnosis and to monitor responses to therapy for many viral infections, has also revolutionized posttransplant care.

References

1. Fishman JA. From the classic concepts to modern practice. Clin Microbiol Infect. 2014;20 Suppl 7:4–9.
2. Dharnidharka VR, Agodoa LY, Abbott KC. Risk factors for hospitalization for bacterial or viral infection in renal transplant recipients–an analysis of usrds data. Am J Transplant. 2007;7:653–61.
3. Wang SF, Huang ZY, Chen XP. Biliary complications after living donor liver transplantation. Liver Transpl. 2011;17:1127–36.
4. DeOliveira ML, Jassem W, Valente R, et al. Biliary complications after liver transplantation using grafts from donors after cardiac death: results from a matched control study in a single large volume center. Ann Surg. 2011;254:716–22; discussion 722–13.
5. Arnow PM, Zachary KC, Thistlethwaite JR, Thompson KD, Bova JL, Newell KA. Pathogenesis of early operative site infections after orthotopic liver transplantation. Transplantation. 1998;65:1500–3.
6. Lo A, Stratta RJ, Hathaway DK, et al. Long-term outcomes in simultaneous kidney-pancreas transplant recipients with portal-enteric versus systemic-bladder drainage. Am J Kidney Dis. 2001;38:132–43.
7. Akhter K, Timpone J, Matsumoto C, Fishbein T, Kaufman S, Kumar P. Six-month incidence of bloodstream infections in intestinal transplant patients. Transpl Infect Dis. 2012;14:242–7.
8. Guaraldi G, Cocchi S, Codeluppi M, et al. Outcome, incidence, and timing of infectious complications in small bowel and multivisceral organ transplantation patients. Transplantation. 2005;80:1742–8.

9. Middleton SJ, Jamieson NV. The current status of small bowel transplantation in the uk and internationally. Gut. 2005;54:1650–7.
10. Giani T, Conte V, Mandala S, et al. Cross-infection of solid organ transplant recipients by a multidrug-resistant klebsiella pneumoniae isolate producing the oxa-48 carbapenemase, likely derived from a multiorgan donor. J Clin Microbiol. 2014;52:2702–5.
11. Mueller NJ, Weisser M, Fehr T, et al. Donor-derived aspergillosis from use of a solid organ recipient as a multiorgan donor. Transpl Infect Dis. 2010;12:54–9.
12. Huprikar S, Bosserman E, Patel G, et al. Donor-derived trypanosoma cruzi infection in solid organ recipients in the united states, 2001–2011. Am J Transplant. 2013;13:2418–25.
13. Ison MG, Grossi P. Donor-derived infections in solid organ transplantation. Am J Transplant. 2013;13 Suppl 4:22–30.
14. Lortholary O, Charlier C, Lebeaux D, Lecuit M, Consigny PH. Fungal infections in immunocompromised travelers. Clin Infect Dis. 2013;56:861–9.
15. Giannella M, Munoz P, Alarcon JM, Mularoni A, Grossi P, Bouza E. Pneumonia in solid organ transplant recipients: a prospective multicenter study. Transpl Infect Dis. 2014;16:232–41.
16. Fishman JA. From the classic concepts to modern practice. Clin Microbiol Infect. 2014;20 Suppl 7:4–9.
17. Bartoletti M, Giannella M, Caraceni P, et al. Epidemiology and outcomes of bloodstream infection in patients with cirrhosis. J Hepatol. 2014;61(1):51–8.
18. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med. 2007;357:2601–14.
19. McKinnell JA, Cannella AP, Kunz DF, et al. Pneumocystis pneumonia in hospitalized patients: a detailed examination of symptoms, management, and outcomes in human immunodeficiency virus (hiv)-infected and hiv-uninfected persons. Transpl Infect Dis. 2012;14:510–8.
20. San Juan R, Aguado JM, Lumbreras C, et al. Incidence, clinical characteristics and risk factors of late infection in solid organ transplant recipients: data from the resitra study group. Am J Transplant. 2007;7:964–71.
21. Bate SL, Dollard SC, Cannon MJ. Cytomegalovirus seroprevalence in the united states: the national health and nutrition examination surveys, 1988–2004. Clin Infect Dis. 2010;50:1439–47.
22. Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. Rev Med Virol. 2010;20:202–13.
23. Kotton CN, Kumar D, Caliendo AM, et al. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation. 2013;96:333–60.
24. Husain S, Pietrangeli CE, Zeevi A. Delayed onset cmv disease in solid organ transplant recipients. Transpl Immunol. 2009;21:1–9.
25. Cervera C, Fernandez-Ruiz M, Valledor A, et al. Epidemiology and risk factors for late infection in solid organ transplant recipients. Transpl Infect Dis. 2011;13:598–607.
26. Razonable RR. Strategies for managing cytomegalovirus in transplant recipients. Expert Opin Pharmacother. 2010;11:1983–97.
27. Razonable RR. Cytomegalovirus infection after liver transplantation: current concepts and challenges. World J Gastroenterol. 2008;14:4849–60.
28. Razonable RR. Management strategies for cytomegalovirus infection and disease in solid organ transplant recipients. Infect Dis Clin N Am. 2013;27:317–42.
29. Florescu DF, Qiu F, Schmidt CM, Kalil AC. A direct and indirect comparison meta-analysis on the efficacy of cytomegalovirus preventive strategies in solid organ transplant. Clin Infect Dis. 2014;58:785–803.
30. Abate D, Saldan A, Fiscon M, et al. Evaluation of cytomegalovirus (cmv)-specific t cell immune reconstitution revealed that baseline antiviral immunity, prophylaxis, or preemptive therapy but not antithymocyte globulin treatment contribute to cmv-specific t cell reconstitution in kidney transplant recipients. J Infect Dis. 2010;202:585–94.
31. Gerna G, Lilleri D, Chiesa A, et al. Virologic and immunologic monitoring of cytomegalovirus to guide preemptive therapy in solid-organ transplantation. Am J Transplant. 2011;11: 2463–71.

32. Allen UD, Preiksaitis JK. Epstein-barr virus and posttransplant lymphoproliferative disorder in solid organ transplantation. Am J Transplant. 2013;13 Suppl 4:107–20.
33. Caillard S, Lamy FX, Quelen C, et al. Epidemiology of posttransplant lymphoproliferative disorders in adult kidney and kidney pancreas recipients: report of the french registry and analysis of subgroups of lymphomas. Am J Transplant. 2012;12:682–93.
34. Gulley ML, Swinnen LJ, Plaisance Jr KT, Schnell C, Grogan TM, Schneider BG. Tumor origin and cd20 expression in posttransplant lymphoproliferative disorder occurring in solid organ transplant recipients: implications for immune-based therapy. Transplantation. 2003;76:959–64.
35. Olagne J, Caillard S, Gaub MP, Chenard MP, Moulin B. Post-transplant lymphoproliferative disorders: determination of donor/recipient origin in a large cohort of kidney recipients. Am J Transplant. 2011;11:1260–9.
36. Wilck MB, Zuckerman RA. Herpes simplex virus in solid organ transplantation. Am J Transplant. 2013;13 Suppl 4:121–7.
37. Hirsch HH, Randhawa P. Bk polyomavirus in solid organ transplantation. Am J Transplant. 2013;13 Suppl 4:179–88.
38. Cervera C, van Delden C, Gavalda J, Welte T, Akova M, Carratala J. Multidrug-resistant bacteria in solid organ transplant recipients. Clin Microbiol Infect. 2014;20 Suppl 7:49–73.
39. Asensio A, Ramos A, Cuervas-Mons V, et al. Effect of antibiotic prophylaxis on the risk of surgical site infection in orthotopic liver transplant. Liver Transpl. 2008;14:799–805.
40. Ramos A, Asensio A, Munez E, et al. Incisional surgical site infection in kidney transplantation. Urology. 2008;72:119–23.
41. Kusne S. Regarding the risk for development of surgical site infections and bacterial prophylaxis in liver transplantation. Liver Transpl. 2008;14:747–9.
42. Grossi PA, Fishman JA. Donor-derived infections in solid organ transplant recipients. Am J Transplant. 2009;9 Suppl 4:S19–26.
43. Bishara J, Goldberg E, Lev S, Singer P, Ashkenazi T, Cohen J. The utilization of solid organs for transplantation in the setting of infection with multidrug-resistant organisms: an expert opinion. Clin Transplant. 2012;26:811–5.
44. San-Juan R, Aguado JM, Lumbreras C, et al. Selective intestinal decontamination with fluoroquinolones for the prevention of early bacterial infections after liver transplantation. Liver Transpl. 2011;17:896–904.
45. Satlin MJ, Jenkins SG, Walsh TJ. The global challenge of carbapenem-resistant enterobacteriaceae in transplant recipients and patients with hematologic malignancies. Clin Infect Dis. 2014;58:1274–83.
46. Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Outcomes of carbapenem-resistant klebsiella pneumoniae infection and the impact of antimicrobial and adjunctive therapies. Infect Control Hosp Epidemiol. 2008;29:1099–106.
47. Clancy CJ, Chen L, Shields RK, et al. Epidemiology and molecular characterization of bacteremia due to carbapenem-resistant klebsiella pneumoniae in transplant recipients. Am J Transplant. 2013;13:2619–33.
48. Bergamasco MD, Barroso Barbosa M, de Oliveira GD, et al. Infection with klebsiella pneumoniae carbapenemase (kpc)-producing k. Pneumoniae in solid organ transplantation. Transpl Infect Dis. 2012;14:198–205.
49. Tacconelli E, Cataldo MA, Dancer SJ, et al. Escmid guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant gram-negative bacteria in hospitalized patients. Clin Microbiol Infect. 2014;20 Suppl 1:1–55.
50. van Duin D, van Delden C. Multidrug-resistant gram-negative bacteria infections in solid organ transplantation. Am J Transplant. 2013;13 Suppl 4:31–41.
51. Lubbert C, Faucheux S, Becker-Rux D, et al. Rapid emergence of secondary resistance to gentamicin and colistin following selective digestive decontamination in patients with kpc-2-producing klebsiella pneumoniae: a single-centre experience. Int J Antimicrob Agents. 2013;42:565–70.
52. Giannella M, Bartoletti M, Morelli MC, et al. Infection with klebsiella pneumoniae carbapenemase producing k. Pneumoniae (kpc-kp) after orthotopic liver transplantation (olt): a risk score. Oral Communication at ICAAC 2014 Washington DC September 5–9 2014. 2014.

53. Simkins J, Muggia V, Cohen HW, Minamoto GY. Carbapenem-resistant klebsiella pneumoniae infections in kidney transplant recipients: a case-control study. Transpl Infect Dis. 2014; 16(5):775–82.
54. Petrosillo N, Giannella M, Lewis R, Viale P. Treatment of carbapenem-resistant klebsiella pneumoniae: the state of the art. Expert Rev Anti Infect Ther. 2013;11:159–77.
55. Viale P, Giannella M, Lewis R, Trecarichi EM, Petrosillo N, Tumbarello M. Predictors of mortality in multidrug-resistant klebsiella pneumoniae bloodstream infections. Expert Rev Anti Infect Ther. 2013;11:1053–63.
56. Bouza E. Consequences of clostridium difficile infection: understanding the healthcare burden. Clin Microbiol Infect. 2012;18 Suppl 6:5–12.
57. Dubberke ER, Burdette SD. Clostridium difficile infections in solid organ transplantation. Am J Transplant. 2013;13 Suppl 4:42–9.
58. Hsu JL, Enser JJ, McKown T, et al. Outcomes of clostridium difficile infection in recipients of solid abdominal organ transplants. Clin Transplant. 2014;28:267–73.
59. Bouza E, Munoz P, Alonso R. Clinical manifestations, treatment and control of infections caused by clostridium difficile. Clin Microbiol Infect. 2005;11 Suppl 4:57–64.
60. Bauer MP, Kuijper EJ, van Dissel JT. European society of clinical microbiology and infectious diseases (escmid): treatment guidance document for clostridium difficile infection (cdi). Clin Microbiol Infect. 2009;15:1067–79.
61. Cornely OA. Current and emerging management options for clostridium difficile infection: what is the role of fidaxomicin? Clin Microbiol Infect. 2012;18 Suppl 6:28–35.
62. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent clostridium difficile. N Engl J Med. 2013;368:407–15.
63. Singh N, Paterson DL. Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management. Clin Infect Dis. 1998;27:1266–77.
64. Bumbacea D, Arend SM, Eyuboglu F, et al. The risk of tuberculosis in transplant candidates and recipients: a tbnet consensus statement. Eur Respir J. 2012;40:990–1013.
65. Keating MR, Daly JS. Nontuberculous mycobacterial infections in solid organ transplantation. Am J Transplant. 2013;13 Suppl 4:77–82.
66. Silveira FP, Husain S. Fungal infections in solid organ transplantation. Med Mycol. 2007;45:305–20.
67. Neofytos D, Fishman JA, Horn D, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. Transpl Infect Dis. 2010;12:220–9.
68. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the transplant-associated infection surveillance network (transnet). Clin Infect Dis. 2010;50:1101–11.
69. Silveira FP, Kusne S. Candida infections in solid organ transplantation. Am J Transplant. 2013;13 Suppl 4:220–7.
70. Singh N, Husain S. Aspergillosis in solid organ transplantation. Am J Transplant. 2013;13 Suppl 4:228–41.
71. Patterson TF. Approaches to fungal diagnosis in transplantation. Transpl Infect Dis. 1999;1:262–72.
72. Cruciani M, Mengoli C, Malena M, Bosco O, Serpelloni G, Grossi P. Antifungal prophylaxis in liver transplant patients: a systematic review and meta-analysis. Liver Transpl. 2006;12:850–8.
73. Lafaurie M, Lapalu J, Raffoux E, et al. High rate of breakthrough invasive aspergillosis among patients receiving caspofungin for persistent fever and neutropenia. Clin Microbiol Infect. 2010;16:1191–6.
74. Giannella M, Ercolani G, Cristini F, et al. High-dose weekly liposomal amphotericin b antifungal prophylaxis in patients undergoing liver transplantation: a prospective phase ii trial. Transplantation. 2015;99(4):848–54.
75. Bassetti M, Marchetti M, Chakrabarti A, et al. A research agenda on the management of intra-abdominal candidiasis: results from a consensus of multinational experts. Intensive Care Med. 2013;39:2092–106.

76. Singh N, Limaye AP, Forrest G, et al. Combination of voriconazole and caspofungin as primary therapy for invasive aspergillosis in solid organ transplant recipients: a prospective, multicenter, observational study. Transplantation. 2006;81:320–6.
77. Len O, Garzoni C, Lumbreras C, et al. Recommendations for screening of donor and recipient prior to solid organ transplantation and to minimize transmission of donor-derived infections. Clin Microbiol Infect. 2014;20 Suppl 7:10–8.

Donor Selection, Evaluation, and Management

3

Alessandro Nanni Costa

3.1 Introduction

In 50 years, transplants have become an established and highly successful clinical practice throughout the world, an effective and irreplaceable treatment practice.

This notwithstanding, increased use of this treatment opportunity, for which the clinical complications and contraindications are steadily reducing in number, is still being held back by the scarcity of available donors.

The value of donating a part of your body is more than we might commonly imagine. However, a donation mind-set certainly cannot be imposed through rules or laws, because nothing can be introduced in law that has not first entered our consciousness.

3.2 Organizational and Management Aspects of the Italian System

The subject of donations in Italy cannot be addressed without first describing the National Transplant Network and its mission. The current system was formally established following the approval of *Law 91 of 1 April 1999* [1] which, by clearly defining the roles, functions, and responsibilities involved, paved the way for a reorganization of the entire national system, bringing undeniable improvements to the existing framework. Of the many provisions contained in this law, the organizational aspects are most definitely a central theme – a theme to which all of ten articles are devoted. For the first time in Italian legislation, Law 91/1999 sanctioned the

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principle that "organ and tissue transplants and their coordination are an objective of the National Health Service."

The *coordination centers* therefore acquired an essential role in the system. They form the backbone of the National Transplant Network and, with due consideration for the different contexts in which they operate, identify with and share a common sense of belonging to a network; an ability to manage sensitive care processes; a responsibility to ensure that procedures meet high quality and safety standards; and a determination to provide treatment opportunities ever more closely aligned with the needs of patients on waiting lists.

Other important points are the implementation provisions regarding the declaration of consent to the removal of organs and tissues [2, 3] and the training of healthcare professionals.

In reorganizing the system, the *National Transplant Center* (CNT) was, undoubtedly, one of the most important innovations introduced by the law.

Law 91/1999 entrusted the CNT not just with the national coordination of organ, tissue, cell donation and transplant activity at the national level but also, with monitoring transplants and waiting lists through the donation information system. The CNT drew up guidelines and operational protocols, allocating organs for urgent cases referred to the national pool, drawing up parameters to evaluate the quality and results of transplant facilities, and promoting and coordinating relations with foreign institutions operating in the sector. Other tasks envisaged by the law include collaboration in awareness-raising initiatives, managing the information system, and, more in general, playing an effective role in the organizational and management functions of the transplant system.

3.3 Sources of Organs for Transplant

Most of the transplants performed throughout the world use *cadaver donors* as their primary source of organs and tissues. This vital resource, which is, unfortunately, never sufficient to cover the needs of all the patients on the waiting lists, can be used in Italy only if two conditions are satisfied: the irreversible cessation of all *brain functions* and non-opposition expressed by the subject while living or by his or her family members entitled to do so.

Diagnosis of death is, therefore, the necessary clinical condition to begin the donation process. Death can be confirmed using two different criteria: the neurological criterion and the cardiocirculatory criterion. Both are independent of the removal and transplant procedures; they are obligatory by law in all cases; they are regulated by specific, mandatory provisions [1, 4–7]; and they are accompanied by implementation regulations and reference guidelines [8].

Once death has been confirmed, irrespective of whether a donation can be made, the family cannot oppose the suspension of any procedures being performed at that time. The body of the deceased is prepared, with the utmost respect and dignity, for the funeral and mourning process.

The other source of organs is donation by *living donors*. This, it should be noted, is in addition to and not in place of donation from cadavers.

It is without a doubt in liver transplants that we have seen the most notable development in surgical technique, the "split liver." This makes it possible to remove a portion of the living adult donor's liver and transplant it, generally into a child [9] but in many cases into an adult [10, 11]. Today, this procedure accounts for about 2 % of all liver transplants. In most cases, it is performed on blood relatives (Table 3.1), and even though its frequency has fluctuated over the years (Fig. 3.1), it has become an established part of the repertoire of a number of transplant centers.

Italy currently has living donor programs for kidney, liver, lung, pancreas, and intestinal transplants. Donation from living donors is regulated by a number of provisions and accompanied by numerous guidance documents and ethical statements

Table 3.1 Liver transplants from living donors: donor-recipient relationship

	No. of cases	Percentage (%)
Blood relatives		
Children	157	51.8
Siblings	43	14.2
Mother	27	8.9
Father	20	6.6
Half-siblings	9	3.0
Other degrees of kinship	4	1.3
Twins	2	0.7
	262	**86.5**
Non-blood relatives		
Spouses	27	8.9
Acquaintances	6	2.0
Domino transplants	3	1.0
Relations by marriage	3	1.0
Cohabiting partners	2	0.7
	41	**13.5**

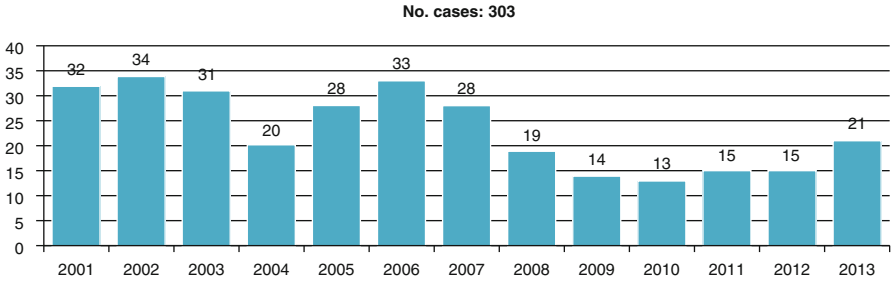

Fig. 3.1 Liver transplants from living donors 2011–2013

[12–16]. The feasibility procedures are very rigid and require a number of examinations, both clinical and motivational. The latter are conducted by a third-party commission [15] independently of the recipient's treatment team (transplant surgeon, nephrologist, etc.).

In no case does donation give rise to direct or indirect payment or to benefits of any kind. Moreover, consent may be withdrawn at any moment, up until the time of the transplant itself. In urgent cases, for which the allocation of organs from cadavers is given priority at the national level, transplants of organs or parts of organs from living donors are not allowed.

3.4 Descriptive Epidemiology of Donations in Italy

In 2000, Italy had an average of 14.3 *donors used* per million population (p.m.p.) but showed clear and notable differences between the north (21.9 donors p.m.p.) and south (6.0 p.m.p.) of the country. Since then, the number of donors has increased by 4.2 p.m.p. to 18.5 in 2013, but the north-south gap has remained more or less unchanged, notwithstanding the rise in absolute numbers. Certain "virtuous" regions demonstrate that a level of 30–40 donors used p.m.p. is not just a chimera: examples are Tuscany, with 35.1 donors p.m.p.; Piedmont, with 30.2; and Friuli-Venezia Giulia, with 27.1. Other regions, however, are clearly, and objectively, lagging behind: Calabria, with 9.2; Puglia, with 8.6; Basilicata, with 6.9; Campania, with 6.6; and Molise, with 3.2 p.m.p (Fig. 3.2).

This gap is the principal challenge in the system and prevents us from realizing the concept of social equity and equality of access to the treatment that patients

Year 2000

Geographic area	Utilized no. of donors	P.M.P. per million of population
Nord	564	21.9
Centro	134	12.1
Sud e Isole	125	6.0
Italia	**823**	**14**

Fig. 3.2 Donors used p.m.p. by geographical region 2000 vs. 2013. Anno 2000 = Year 2000/Anno 2013 = Year 2013/Area geografica – Geographical Region, Donatori utilizzati – Donors used/Nord = North/Centro = Center/Sud e Isole = South and Islands, Italia = Italy – P.M.P. (21.9/12.1/6.0/14.3)

need. On the contrary, it gives rise to, and encourages, flows of patients from the south of the country to regions with better provision. And to a certain degree (fortunately less than in the past), it invites them to seek a solution – one that is not devoid of risks – abroad.

The initiatives undertaken over the years, including the action taken on health planning in a number of regions by pressing for higher donation rates to be given prominence in regional health plans or the temporary transfer of experts from benchmark regional coordination units to those experiencing greater difficulties, have undoubtedly led to an overall improvement in activity levels. A resource-distribution system to provide support for donation and transplant activities has also been proposed and implemented, following an approach that does not simply include but indeed focuses on achieving the objectives. But the different environmental, organizational, and social situations found in the north and south of the country probably still exert a significant influence.

Another factor of interest concerns the *causes of death* of the donors reported. In the early 2000s, death from vascular causes accounted for 64.38 % of all causes, head injury for 27.26 %, post-anoxia 4.31 %, primary brain tumors 0.99 %, and all other causes 3.03 % (Table 3.2). The epidemiological data for 2013 indicate that in the donors reported, deaths from vascular causes had risen to 69.82 % (an increase of 5.44 %), while those from head injury had fallen to 16.07 % (a decrease of 11.19 %). Other causes remained more or less unchanged (Table 3.3).

These figures are in line with the aging of the general population, in which vascular accidents are undoubtedly more frequent. But they also point to the fact that many potential donors are moving into the "senior" age group, a factor that in future could have a growing impact and which will need to be addressed more and more frequently. We will examine this question more closely later. The reduction in the number of deaths from head injuries should, however, provide some cause for relief, as this type of event is typical of the young and very young.

Table 3.2 Causes of death of donors reported in 2002

	Vascular		Head injury		Post-anoxia		Brain tumor		Others	
	No.	%	No.	%	No.	%	No.	%	No.	%
North	590	34.44	254	14.82	42	2.45	9	0.52	29	1.69
Center	248	14.47	88	5.13	15	0.87	2	0.11	8	0.46
South/islands	265	15.46	125	7.29	17	0.99	6	0.35	15	0.87
Total	**1,103**	**64.38**	**467**	**27.26**	**74**	**4.31**	**17**	**0.99**	**52**	**3.03**

Table 3.3 Causes of death of donors reported in 2013

	Vascular		Head injury		Post-anoxia		Brain tumor		Others	
	No.	%	No.	%	No.	%	No.	%	No.	%
North	785	34.58	164	7.22	114	5.02	7	0.30	49	2.15
Center	430	18.94	105	4.62	46	2.02	6	0.26	30	1.32
South/islands	370	16.29	96	4.22	37	1.62	10	0.44	21	0.92
Total	**1,585**	**69.82**	**365**	**16.07**	**197**	**8.67**	**23**	**1.01**	**100**	**4.40**

The conclusions to be drawn from these figures become less direct if we analyze them from a geographical perspective. Indeed, if we evaluate the incidence of the various *causes of death* in the north, center, and south and islands of the country, it becomes difficult, frankly, to understand why, in the period from 2002 to 2013, out of a total of 17,127 potential donors who died from vascular causes, 32.64 % were reported in the north and just over 15 % in the center and south (17.62 % and 16.51 %, respectively) (Table 3.4). The explanation could lie in the higher concentration of elderly people in the north than in the center and in the south and islands, but in this case the figures would run counter to the country's general demographic trends, which see higher longevity rates in the center-south and islands [17]. Or it could lie in differences of approach in identifying and reporting these potential donors. This seems to us to be the most probable cause, but the figures undoubtedly merit further study.

Another factor of interest, as we have just mentioned, is the *age of the donors* reported and how this has changed over time. To give this variation its due prominence, we considered the donors used. In 2002, their mean age was 47.1 years and the median was 51. By 2013, the average age had risen to 57.5 and the median to 62. In practice, the population of donors used has "aged" over the period by 10 years (average value) and 11 years (median value) (Fig. 3.3).

Table 3.4 Causes of death of the 25,646 donors reported from 2002 to 2013

	Vascular		Head injury		Post-anoxia		Brain tumor		Others	
	No.	%	No.	%	No.	%	No.	%	No.	%
North	8,371	32.65	2,772	10.86	939	1.31	99	0.38	534	0.98
Center	4,521	17.62	1,338	5.21	300	0.39	70	0.27	264	0.36
South/islands	4,235	16.51	1,478	5.76	245	0.34	68	0.26	312	0.43
Total	**17,127**	**66.78**	**5,588**	**21.78**	**1,484**	**5.78**	**237**	**0.92**	**1,210**	**4.71**

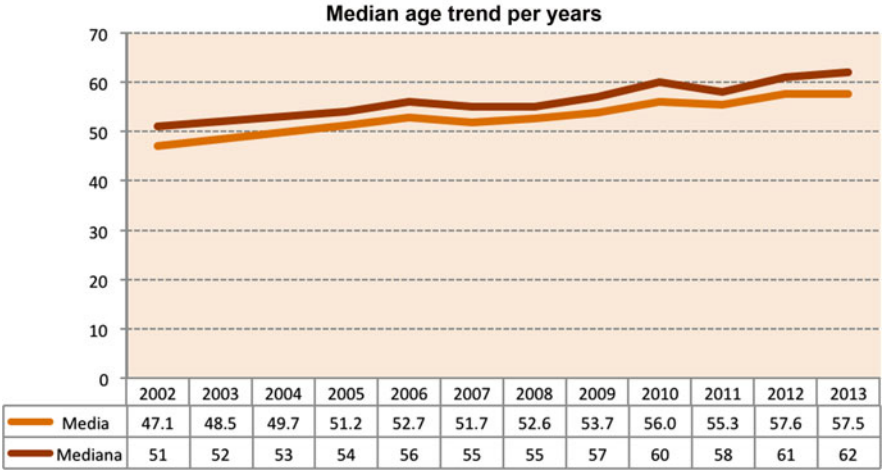

Fig. 3.3 Mean and median age of donors used; mean and median age over time. Media, mean; mediana, median

Experience tells us that if we raise the bar of the donors' age limit, the number of donations increases and with it the number of organs, most notably liver and kidneys, available for transplant. The noteworthy factor here is that the outcome of these transplants does not appear to be significantly influenced by the donor's age, at least in the short and medium term. The risk of occult malignancies could be higher in older individuals, but considering the strategies implemented (safety guidelines and second opinions), this is highly unlikely and, ultimately, in the risk-benefit ratio, the balance most definitely tips in favor of the transplant.

In any case, the factor indicating the age limit or suitability (or lack thereof) of an organ should not be the donor's date of birth but the organ's functional reserve. From the legislative point of view, there is no age limit to donation. Where to set the acceptability bar is, therefore, a question that involves balancing medical judgment and the informed consent of the patient, with respect both to the known risks and to any unknown risks that might emerge following the transplant [18].

3.5 Search and Selection Strategies

To improve the process of searching for and identifying all potential donors, we need to identify and monitor the channels through which neurologically injured patients normally pass when receiving first aid in hospital. This provides us with real-time information about patients who could potentially become donors and their exact location in the hospital. The strategies for monitoring these patients require the constant monitoring of their clinical course.

To this end, collaboration with the Health Directorate and the Instrumental Diagnostics Services (neuroradiology, CAT) is a vital element in providing us with an overview of neurologically injured patients whose clinical progress is to be monitored from day to day. Access to the data on deaths occurring in the various wards during the previous 24 h is equally useful as a way of identifying all potential tissue donors.

For this purpose, some years ago, the Italian system set up a *National Register of Deaths from brain injuries*, with the aim of providing prospective evidence not just of the clinical epidemiology of patients in intensive care with acute brain injuries but also of the efficiency of the entire donation process.

Identifying potential organ donors in intensive care is, in fact, the key point and essential precondition for donation activity. Collecting specific data, such as the numbers of deaths from brain injuries and of brain-stem deaths, hospital beds, and actual donors, has made it possible to construct simple outcome and process indicators to determine and analyze the various stages in the process as a whole.

On the basis of the results obtained, we have therefore been able to identify training needs, organizational support, and the critical points of the donation process at the point of identifying the potential donor. Constant monitoring using centralized online data on brain injury deaths in intensive care is also proving to be a sensitive and objective tool in evaluating and planning improvements from the logistical-organizational, structural, and staff-training perspectives.

The efficiency of the procurement process and related individual logistical-organizational factors has been and continues to be evaluated regularly, including through audits. In the framework of the National Quality Program, the National Transplant Center plans to extend this evaluation process to local coordination units by verifying qualitative and quantitative features in individual hospitals, using specific indicators for each sphere of evaluation.

Through this initiative, it has been possible to arrive at an accurate and detailed assessment of the level of the donation system in Italy by evaluating individual situations and viewing them in context. Creating an objective way to evaluate the strong and weak points of the system has been, and will increasingly be, indispensable if we are to introduce the required corrective measures, including by implementing the ambitious project of transferring the know-how of certain advanced treatment centers to others experiencing greater difficulties. This is vital if we are to ensure uniform quality and safety standards and, at the same time, nudge the system toward a better "organ procurement" balance between the different parts of the country.

3.6 Donor Selection and Evaluation Criteria

It is universally recognized that promoting safety and quality in managing delicate healthcare processes is based on a systemic approach that includes the study of noncompliance, the identification of circumstances and factors that may facilitate or actually cause harm to the patient, and the planning of appropriate and effective management and care pathways [19]. More specifically, analyzing the causes and contributing factors is particularly complex but essential to managing the *clinical risk*. The aim of such analysis is to identify the factors that may have contributed to the occurrence of an undesired event, by applying a system- and process-focused investigation methodology [20].

Establishing the causes of adverse events is therefore vital if we are to identify the most appropriate solutions and prevent similar events from occurring in the future [21, 22]. This clearly applies to all donors, whether dead or alive, but with one major difference: in donation from cadavers, everything must be done with the utmost care and attention but in the time frame imposed by the circumstances.

It is in this direction that the National Transplant Center is focusing its efforts with a view to minimizing the risks of organizational and management noncompliance that are typical of complex health systems and of which transplants are undoubtedly the most multifaceted example. In approaching the problem, we therefore took into account the complexity of the system, the multidisciplinary nature of the subject, and, above all, the multiplicity of parties involved.

As a consequence, we deemed it necessary to start from a description of the process (supply chain), an analysis of the decision-making and operational pathways conducted by examining their components (type of situations managed and units participating in the process), and the tasks and operational behavior required (human resources involved, procedures and methods adopted). The aim here was to codify the process and identify its main problem areas [23]. As a further measure to

promote safety, appropriate guidelines and related specific protocols were issued [24]. These were designed to illustrate even more clearly to the professionals working in the network the intrinsic problems and the professional rules that must be followed if they are to perform their mission to best effect.

The *safety guidelines* focus on two main aspects:

1. Describing the different levels of risk defined from the clinical point of view, with due consideration for the ethical implications
2. Indicating the strategies to adopt to increase the rate of early identification of donors at risk of transmitting diseases to recipients

Five different risk levels were thus identified:

Unacceptable risk: Potential donors classified under this risk level are to be ruled out completely. This category includes HIV 1 or 2 seropositivity; HbsAg and HDV contemporaneous seropositivity (hepatitis B and delta coinfection); and current neoplastic conditions, with the exception of carcinoma in situ, basal cell carcinoma, cutaneous squamous cell carcinoma without metastases, carcinoma in situ of the cervix, carcinoma in situ of the vocal cords, and urothelial papillary carcinoma (T0 according to the TNM classification). For other tumors, for which the epidemiological studies indicate that the risk of transmitting the tumor is much lower than the potential benefit to be achieved from the transplant, the transplant center can decide to use the organ, subject to the informed consent of the recipient. Lastly, systemic infections, for which no feasible treatment options are available, and documented prion diseases are also excluded.

Increased but acceptable risk: Cases where the use of organs is justified by the urgency of the case or the specific clinical condition of the recipient. In these cases, even if the evaluation process detects the presence of pathogens or pathologies that could be transmitted through the transplant, the use of the organs in question is allowed in the context of a risk-benefit analysis. Examples are patients affected by fulminant hepatitis, re-transplants for primary loss of hepatic function, or patients undergoing hepatectomy with total loss of liver function. In all of these cases, a transplant is the only possibility of saving the patient and so the use of the organ, even if not optimal, is justified.

Calculated risk: Cases where the presence of a pathogen or serological status in the donor is compatible with a transplant in recipients with the same pathogen or serological status. Distinctions are of course made, with respect both to the organs that can be used (liver, kidney, heart, lung) and to the pathogen or serological status affecting them (HBsAg+ or anti-HCV+, or HbcAb donors, etc.). Depending on the case, these organs can be used subject to the informed consent of the recipient and to compliance with specific diagnostic and treatment protocols to monitor the transplant. These cases are described in detail in the guidelines and in the protocols to which healthcare professionals refer and which it is not possible to set out in detail here.

However, for an idea of the types of cases referred to, we need only to consider recipients with liver cirrhosis secondary to HCV infection, which is the main indication for liver transplants. The HCV infection recurs after the transplant in nearly all cases, but the short- and medium-term survival rates are excellent. Studies have shown that anti-HCV-positive donors can be considered suitable for liver transplants in recipients with the same serological agent, if the HCV infection in the donor has not caused irreversible hepatic histological damage such as fibrosis [25]. This means that today, these organs, which were previously deemed unsuitable, can be used, and by no means a negligible number of usable organs can be recovered for transplant.

Non-assessable risk: Cases where the evaluation process does not enable the risk to be adequately assessed because one or more of the assessment factors are not available (e.g., accurate medical history). In such cases, for the donor to be considered suitable, tests and investigations will have to be carried out to verify whether any of the absolute exclusion factors or other, relative, contraindications apply (infectious disease biomolecular tests conducted by laboratories with the appropriate specialist expertise and experience in the sector, so as to reduce the "window period" as much as possible; subsequent *postmortem* examination).

One example of potentially high non-assessable risk for infectious diseases is the West Nile virus (WNV). After the outbreak in 1998, the Italian Ministry of Health decided to set up a National Surveillance Plan regulated by the ministerial circular on "Sorveglianza dei casi umani delle malattie trasmesse da vettori con particolare riferimento alla Chikungunya, Dengue e West Nile Disease" (surveillance of human cases of diseases transmitted by carriers with particular reference to Chikungunya, Dengue, and West Nile Disease – 2013 update) [26]. The timescale for the epidemiological surveillance of human cases of these diseases extends throughout the year. However, in the period of carrier activity (15 June to 30 November), the surveillance system must be ready for prompt and timely action so that the necessary checks can be carried out.

On the basis of the epidemiological surveillance data of human cases of neuroinvasive WNV diseases and of virus circulation in the year immediately preceding the occurrence, each year the National Transplant Center issues a number of actions to be taken to prevent the transmission of WNV through organ, tissue, or cell transplants and to promptly identify any transplants from WNV-positive donors.

In the case of organ transplants from cadaver donors, it is recommended to carry out the Nucleic Acid Test (NAT) for WNV in the 72 h following donation, on all donors who had been resident in the regions affected and all donors who, on the basis of investigation into their medical history, had spent at least one night in the regions affected during the previous 28 days. If the test turns out to be positive, the National Transplant Center (CNT), the interregional transplant centers (ITC), and the regional transplant centers (RTC) concerned must be informed.

For transplants from living donors, it is recommended to carry out the Nucleic Acid Test for WNV before the transplant is performed, on all donors resident in the regions affected and all donors who, on the basis of investigation into their

medical history, have spent at least one night in the regions affected during the previous 28 days. If the test turns out to be positive, the CNT, the ITC, and the RTC concerned must be informed.

If, on the other hand, the tests are negative, the donor may be considered as presenting a "standard risk." If for some reason the tests cannot be carried out, the donor must only be used in urgent cases, or where the recipient has a specific medical condition, subject to his or her informed consent.

Standard risk: Cases where no risk factors for transmissible diseases are identified in the evaluation process and the most frequent condition in the evaluation process for donors and individual organs. This level of risk is commonly described as "standard" for the simple fact that, in the transplant discipline, there is no such thing as "*zero risk*." This is because the possibility of transmitting both infectious and neoplastic diseases is always present, even if the guidelines are followed and/or professional conduct complies with good clinical practice. That said, it cannot be denied that the rigorous application of the guidelines in routine practice minimizes the possible risk factors or at least pinpoints them so that they can be better assessed and, if possible, overcome.

As regards measures to reduce the use of donors with occult malignancies, the document identifies two distinct stages:

1. *Risk evaluation process* prior to removal (medical history, physical examination, instrumental and laboratory tests)
2. Risk evaluation process during removal (checking up on all the potential signs observed in the previous stages, inspection and palpation of organs and lymph node stations, systematic decapsulation of the kidney at the time of removal)

In our experience, the guidelines and related protocols have proved to be a vital tool to guide healthcare professionals through the large amounts of unfiltered information, often of dubious utility, and help them make their clinical decisions. They provide a valuable reference tool for a profession increasingly having to select from multiple and variable possible solutions to the same type of problem. Intended as general recommendations and scientific aids for healthcare professionals, the guidelines focus on frequent and significant situations they are likely to encounter. They were drawn up through discussions between experts and professionals with support from the international literature and are designed to help healthcare professionals select the most effective and appropriate solutions to resolve the problems to be tackled.

The endpoint of the guidelines and related operational protocols is to increase the treatment options for patients on the transplant waiting list by using donors who just a few years ago would have been rejected but without exposing the recipients to unacceptable risks. This is achieved by informing healthcare professionals of the most accredited assessment methods already formulated at the scientific level and validated through the consensus conference system. In this framework, the reference to *evidence-based medicine* (EBM) must be interpreted as an authoritative

invitation to make an informed and well-documented choice from generally accredited diagnostic and treatment pathways and to accurately record the options adopted.

The fact remains, however, that in the donation-transplant process, even if healthcare professionals follow the guidelines and good clinical practice, the risk of noncompliance or of the transmission of disease from donor to recipient is always present. With this in mind, the National Transplant Center has set up a group of expert clinicians (medical examiner, anatomo-pathologist, infectivologist, immunologist) to supplement the guidelines and good clinical practice. The group is available 24 h a day and can be contacted by the network for a second opinion in cases where doubts may arise as to the correct interpretation of a case. This pool of experts has further helped transmit an enhanced culture of safety throughout the system, not least by providing reassurance in doubtful cases. It has also made it possible to substantially increase the use of donors with evident risk factors.

But we did not only provide the network with recommendations as to the optimal procedures and conduct to follow. In the knowledge that in the world of transplants the best possible outcomes are obtained through procedures that are not just effective but also, and increasingly, familiar and safe, we felt it necessary to produce tools, and introduce them in routine professional practice, that would enable healthcare professionals to identify, classify, and analyze the causes of undesired events. With this in mind, we embarked on a quality and safety pathway that has enabled us to design a model for recording and classifying adverse events and reactions, i.e., those situations which, in the donation and transplant process, are unsatisfactory or deviate from the optimal benchmark model.

In designing this model, we formulated an analysis pathway starting from a description of the principal stages of the donation-removal-transplant process and the professionals involved or units participating in the process (Table 3.5). This enabled us to codify the "supply chain" in all its stages, identify the main problems encountered at each stage, and list the consequences of conduct that fails to comply with the recommended procedures. We then turned our attention to producing a noncompliance assessment and classification matrix based on two variables: *Severity* (insignificant, minor, moderate, major, catastrophic) and *Probability of Recurrence* (unlikely, rare, possible, likely, almost certain) (Table 3.6).

Each of these two variables was assigned a score ranging from 1 to 5 (e.g., for the "Severity" variable, insignificant = 1, minor = 2, moderate = 3, major = 4, and catastrophic = 5). The same principle was adopted for the "Probability of Recurrence" variable (unlikely = 1, rare = 2, possible = 3, likely = 4, and almost certain = 5). The product of these two variables gives us a score that identifies the "weight," or the extent, of the adverse event or reaction.

The "weight" of each score was then illustrated on a "four-color scale" of green, yellow, orange, and red (Table 3.7). The green band shows all events that do not entail consequences or harm to the patient and which feature only marginal noncompliance with the procedures, mainly limited to the operational unit involved. The yellow band includes events for which only one of the two variables is high, with the other insignificant or occurring only rarely. The third, orange, band outlines a very precise alarm zone where the authorities responsible must adopt appropriate

Table 3.5 Principal stages in the donation-removal-transplant process and professionals involved

Stages of process	Professionals and services involved
1. Identification of potential donor	Local coordinator, nurse, intensive care specialist, or other professionals
2. Diagnosis, verification, and certification of death	Intensive care specialist and/or local coordinator, medical commission (medical examiner, intensive care specialist, neurologist)
3. Relevant coordination center notified of potential donor	Intensive care specialist, local coordinator, nurse
4. Initial suitability assessment	Intensive care specialist and/or local coordinator, coordination authorities (RTC/ITC), second opinion
5. Donor maintenance	Intensive care specialist, local coordinator, nurse
6. Discussion with family	Intensive care specialist and/or local coordinator, nurse
7. Sampling of lymph nodes and/or peripheral blood for immunological profile	Local coordinator, local surgeon, intensive care specialist, nurse
8. Consultation of lists and allocation of organs	Coordination authorities (RTC/ITC), transplant centers
9. Recipients notified for admission	Transplant centers, coordination centers, transport centers
10. Instrumental and laboratory tests (e.g., biopsies, angiography, CT angiography, coronary angiography, etc.)	Intensive care specialist and/or local coordinator, diagnostic services, healthcare personnel
11. Removal of organs and tissues and second suitability assessment	Removal surgeons, theater personnel, anesthesiology team, coordination authorities, second opinion, diagnostics services, consultants
12. Back table surgery and third suitability assessment	Removal/transplant surgeons, any other specialists, second opinion
13. Transplant	Transplant surgeons, anesthesiology team, diagnostics, and laboratory services
14. Follow-up	Transplant centers and/or specialist units in patient's own health facility, primary care doctors, nurses, diagnostics, and laboratory services
15. Logistics	Cross-cutting process applying to all stages. May involve more than one health facility (local coordination units, regional transplant centers/interregional transplant centers, transplant centers, laboratories)
16. Management of patient during waiting list or posttransplant stages	Transplant centers, regional coordination centers, laboratories, specialist doctors

and timely corrective measures since the noncompliance could recur in a more serious form. The last, red, band includes the highest score produced by the two variables, where the event has caused serious harm to the patient and/or damage to the system.

The next step was to establish an information channel for the structure concerned to inform the competent regional authority (the RTC) of any noncompliance it has

Table 3.6 Matrix for the assessment of the adverse event/reaction and its significance/consequences

Severity	Insignificant	No significant impact or harm to the patient, the system, or healthcare professionals
	Minor	No direct repercussions on the patient, the system, or healthcare professionals caused by the management or procedural error or noncompliance
	Moderate	Only minor clinical or psychological harm to the patient but damage to the system leading to loss of confidence on the part of citizens and healthcare professionals for a limited period
	Major	Direct consequences on the patient which require hospitalization and/or extension of hospital stay and/or medical or surgical intervention to prevent permanent harm. Serious damage to the system, compromising its credibility and requiring time for said credibility to be restored
	Severe	Death and/or any other harm causing injury or permanent invalidity to the patient or placing his or her life in danger (evidence of transmission of infectious or neoplastic disease) and/or irreparable damage to the credibility of the system
Probability of recurrence	Unlikely	Repetition can essentially be ruled out or would be exceptional, given the measures adopted
	Rare	Event possible but not probable – its occurrence would cause surprise and would be the consequence of unfavorable circumstances
	Possible	Situations where the system has objective underlying noncompliance that remains latent until a mistake by the healthcare professional brings it to light
	Likely	The system and operating procedures in place show shortcomings in their overall framework and management that could open the door to the repetition of at-risk situations. If no action is taken, there is a high probability that this could cause very serious damage
	Almost certain	Evident and constant management problems intrinsic to the organizational framework that are not being addressed through preventive or corrective measures. Recurrence is inevitable

found. After evaluating the case, the RTC forwards the information, using a specific reporting form, to the national authority (the CNT). For cases in the orange or red bands, notification is sent immediately, and the reporting form is accompanied by a detailed report on the case.

To minimize any subjective elements that might influence the allocation of a score to a given instance of noncompliance, a group of clinical experts has also been

Table 3.7 Matrix for the assessment of the adverse event/reaction and allocation of scores

Possible recurrence ⇨ / Severity ⇩	SCORE	Slight possible	Possible	Very possible	Rare	Improbable
	SCORE	5	4	3	2	1
Severe	5	25	20	15	10	5 Great
Great	4	20	Moderate			
Moderate	3	15	12	9	6	3
Minimal	2	10	8	6	4	2
No countable	1	5	4	3	2	1

Probability of recurrence
Pressoché certa = almost certain
Molto probabile = likely
Possibile = possible
Rara = rare
Improbabile = unlikely
Severity
Severa = severe
Maggiore = major
Moderata = moderate
Minore = minor
Insignificante = insignificant

set up. The group includes representatives of the main professions interacting during the donation and transplant process. They share their analyses of the event and together determine how it should be classified (near miss, adverse event, adverse reaction) and allocate the score. The case is then classified on the basis of its type and score and shared with the rest of the National Transplant Network with a view to raising awareness and disseminating a preventive mind-set with respect to such events and an awareness of all the possible corrective measures that can be applied to prevent the problem from recurring.

This has been an undertaking of enormous significance, in cultural, ethical, and social welfare terms – an undertaking through which the National Transplant Center and the network in its entirety have sought to identify any circumstances and factors that might open the way to potential or actual harm to patients and to apply corrective measures to safeguard their health and well-being.

References

1. Law no. 91 of 1 April 1999: "Disposizioni in materia di prelievi e di trapianti di organi e di tessuti" (Provisions concerning the removal and transplantation of organs and tissues). (Italian Official Journal no. 87 of 15 April 1999).
2. Italian Ministry of Health – DECREE of 8 April 2000: "Disposizioni in materia di prelievi e di trapianti di organi e di tessuti, attuativo delle prescrizioni relative alla dichiarazione di volontà dei cittadini sulla donazione di organi a scopo di trapianto" (Provisions concerning the removal and transplantation of organs and tissues, in implementation of the provisions governing citizens' declarations of consent on the donation of organs for transplant purposes). (Italian Official Journal, General Series, no. 89 of 15 April 2000).
3. Italian Ministry of Health – CIRCULAR no. 12 of 30 August 2000: "Indicazioni applicative ed operative per i rianimatori e i coordinatori locali delle attività di prelievo sull' accertamento della manifestazione di volontà alla donazione espressa in vita" (Implementation and operational recommendations for intensive care teams and local coordinators of organ removal procedures concerning the verification of the will to donate expressed during life).
4. Law no. 301 of 12 August 1993: "Norme in materia di prelievi e innesti di cornea" (Provisions governing cornea removal and grafts). (Italian Official Journal no. 192 of 17 August 1993).
5. Law no. 578 of 29 December 1993: "Norme per l'accertamento e la certificazione di morte" (Provisions governing the verification and certification of death). (Italian Official Journal, General Series, no. 5 of 8 January 1994).
6. Italian Ministry of Health – DECREE no. 582 of 22 August 1994: "Regolamento recante le modalità per l'accertamento e la certificazione di morte" (Regulations concerning the arrangements for the verification and certification of death) (Italian Official Journal, General Series, no. 245 of 19 October 1994) as up-dated by the DECREE of 11 April 2008.
7. Decree of 11 April 2008: Up-date of Decree no. 582 of 22 August 1994 regarding "Regolamento recante le modalità per l'accertamento e la certificazione di morte" (Regulations concerning the arrangements for the verification and certification of death). (Italian Official Journal, General Series, no. 136 of 12 June 2008).
8. Linee guida relative all'applicazione delle indagini strumentali di flusso ematico cerebrale in situazioni particolari, ai fini della diagnosi di morte in soggetti affetti da lesioni encefaliche (Guidelines on the application of instrumental investigation of cerebral blood flow in specific situations, for the purpose of diagnosing death in subjects with brain-stem injuries): pursuant to Ministerial Decree no. 582 of 22 August 1994. Permanent Technical Consultation Group, Review of 1 September 2003.
9. Broelsch CE, Whitington PF, Emond JC, Heffron TG, Thistlethwaite JR, Stevens L, Piper J, Whitington SH, Lichtor JL. Liver transplantation in children from living related donors. Surgical techniques and results. Ann Surg. 1991;214:428.
10. Marcos A, Ham JM, Fisher RA, et al. Single-center analysis of the first 40 adult-to-adult living donor liver transplants using the right lobe. Liver Transpl. 2000;6:296–301.
11. Law no. 483 of 16 December 1999: "Norme per consentire il trapianto parziale di fegato" (Provisions to enable partial liver transplants). (Italian Official Journal, General Series, no. 297 of 20 December 1999).
12. Law no. 458 of 26 June 1967: "Trapianto di rene tra persone viventi" (Kidney transplants between living people). (Italian Official Journal no. 160 of 27 June 1967).
13. Linee Guida per il trapianto di fegato da donatore vivente (Guidelines for liver transplants from living donors): Italian Ministry of Health, Higher Council of Health, Section II – March 2001.
14. Linee Guida per il trapianto di fegato da donatore vivente (Guidelines for kidney transplants from living donors) (Standing Conference for Relations between the State, Regions and the Autonomous Provinces of Trento and Bolzano of 31 January 2002). (Italian Official Journal no. 144 of 21 June 2002).

15. “Regolamento per lo svolgimento delle attività di trapianto di organi da donatore vivente” (Regulations for procedures involving transplants from living donors) (Italian Ministry of Health Decree no. 116 of 16 April 2010). (Italian Official Journal, General Series, no. 172 of 26 July 2010).
16. Law no. 167 of 19 September 2013: “Norme per consentire il trapianto parziale di polmone, pancreas e intestino tra persone viventi” (Provisions to enable partial lung, pancreas and intestinal transplants between living people). (Italian Official Journal no. 227 of 28 September 2012).
17. Demographic indicators: ISTAT Censuses 1961-2011 and 1 January 2015–2065. Italia in cifre. Web data: http://www.istat.it/it/files/2011/06/Italia_in_cifre_20132.pdf.
18. Waits SA, Sung RS. Raising the bar for medically complex donors. Transplantation. 2014;97(7):730–1.
19. Frenk J, et al. Health professionals for a new century: transforming education to strengthen health systems in an interdependent world. Lancet. 2010;376(9756):1923–58.
20. Vincent CA. Analysis of clinical incidents: a window on the system not a search for root causes. Qual Saf Health Care. 2004;13(4):242–3.
21. Leape LL MD, et al. The nature of adverse events in hospitalized patients – results of the Harvard Medical Practice Study II. N Engl J Med. 1991;324:377–84.
22. Milch CE, Salem DN, Pauker SG, Lundquist TG, Kumar S, Chen J. Voluntary electronic reporting of medical errors and adverse events an analysis of 92,547 reports from 26 acute care hospitals. J Gen Intern Med. 2006;21(2):165–70.
23. Venettoni S, Rizzato L, Di Ciaccio P, Nanni Costa A. Prevention and management of adverse events in the process of procurement and transplantation of organs: critical elements of the system and clinical governance. Organs Tissues Cells. 2010;2:119.
24. State-Regions Conference of 26 November 2003: “Linee guida per la valutazione di idoneità del donatore e relativi protocolli specifici” (Guidelines on assessing donor suitability and related specific protocols) pursuant to the Ministerial Decree of 2 August 2002 (Italian Official Journal, General Series, no. 297 of 23 December 2003).
25. Pawlotsky JM, Aghemo A, Dusheiko G, Forns X, Puoti M, Sarrazin C. EASL recommendations on treatment of hepatitis C 2014. European Association for the Study of the Liver, International Liver Congress™, Apr 2014.
26. “Sorveglianza dei casi umani delle malattie trasmesse da vettori con particolare riferimento alla Chikungunya, Dengue e West Nile Disease” (Surveillance of human cases of diseases transmitted by carriers with particular reference to Chikungunya, Dengue and West Nile Disease) – 2013 up-date.

The Safety of Donor

4

Antonia D'Errico, Deborah Malvi, and Francesco Vasuri

Safety during organ recruitment means donor safety and organ safety. Efforts to advance transplant safety are ongoing and include improvements to screening tests and checks to detect any kind of donor disease and ensure good graft function after transplantation.

Organ transplantation is the best life-saving treatment for end-stage organ failure. The current organ donor shortage has led to a progressive increase in patients on the waiting lists. Moreover, a long time on the waiting list may result in patients deteriorating or dying before receiving a transplant. In view of this, many transplant centres worldwide have extended their criteria for organ acceptance. Nowadays the donor pool includes older donors, unstable donors, donors with positive viral serology and donors with a history of cancer and in some cases with cancer [1].

4.1 Donor Safety: Transmissible Diseases

4.1.1 Infectious Disease

While reports of infections after tissue transplantation are rare, the true rate of transmission is unknown, although it is estimated in <1 % of solid organ recipients. The risk of infectious transmission has been correlated to microbiological screening, which can vary with national and regional regulations and with the availability and performance of microbiological assays used for potential donors.

Viral, bacterial, parasitic, prion and fungal infections can be transmitted by organs, tissues and cells. Infectious transmissions have often been recognised as

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clusters of infections among recipients of organs from a common donor. These include *Mycobacterium tuberculosis*, *Candida* and *Aspergillus* species, herpes simplex virus and human herpesvirus 8, lymphocytic choriomeningitis virus, rabies virus, HIV and HCV.

Each infectious disease identified in a donor must be treated before organ recruitment: common infections cured before organ donation do not preclude organ transplant. The use of organs from donors with active or suspected infection reflects the urgency of transplantation, the availability of other organs and the recipient's informed consent.

The common screening tests are HBV serology, HIV, HCV, *Toxoplasma*, CMV, EBV panel, herpes simplex virus, varicella-zoster virus antibodies and nontreponemal and treponemal testing. Variations in national guidelines are mainly related to available resources and technologies in the different countries.

General exclusion criteria are rabies, active tuberculosis, HIV or HTLV infection, West Nile virus infection and uncontrolled sepsis. Increased-risk donors include all individuals with uncontrolled sexual behaviour, drug abusers, donors previously treated with human-derived clotting factor concentrates and the prison population. These donors can be considered in a "window period" with very low antibody titres and have to be tested by highly sensitive and specific microbiological assays, such as viral nucleic acid tests [2–5].

4.1.2 Neoplastic Diseases

The transmission of malignancies is a well-recognised complication of transplantation from donors with and without a history of cancer. The employment of older donors has increased the risk of inadvertent cancer transmission. Donor-*transmitted* tumours are those that existed in the donor at the time of transplantation. Donor-derived tumours are de novo tumours that develop in transplanted donor cells. Donor-*transmitted* tumours could be prevented by meticulous donor evaluation.

During the last 10 years, there has been a progressive decrease in the transmission of malignancies, due to the stringent application of guidelines during organ procurement and removal. In 2002 the OPTN/UNOS estimated the risk of cancer transmission to be 0.01 % [6]. In the UK, among 39,765 graft recipients, Desai et al. [7] reported a donor-transmitted cancer in 15 patients (0.05 %) from 13 donors. In no case was cancer detected at the time of transplantation.

Each donor should be investigated for smoking or other cancer related risk factors. If a history of cancer is reported, it is necessary to know the histological diagnosis and the type of tumour, its grading and staging, and the donor's treatment and follow-up. If the donor is a childbearing woman who died from intracranial haemorrhage or had a history of uterine bleeding, all tests to exclude choriocarcinoma must be performed. All donors with intracranial haemorrhage without evidence of arterial hypertension or aneurysms must be evaluated for possible brain metastasis; in some cases, an intraoperative brain biopsy may be required. A meticulous check of the donor's skin can reveal scars or skin lesions suspect for melanoma or a previous melanoma.

Italian guidelines (www.trapianti.salute.gov.it), the Council of Europe [5], Nalesnik et al. [8], and the UK Advisory Committee on the Safety of Blood, Tissues and Organs have defined risk categories for donor tumour transmission. A suggested approach to donor utilisation has been given for each category, recognising the emergent circumstances and clinical urgency. A careful evaluation of the donor before and during organ recruitment is always recommended: [5] palpation of the abdominal organs and lungs, immediate frozen sections of any suspected lesions and preoperative echography of the liver and the kidneys must be performed [9].

The risk profile in the different experiences can be summarised as no significant risk (standard risk), minimal risk, low to intermediate risk, high risk and unacceptable risk. Definition of a risk profile in neoplastic donors is the basis of a careful screening system designed to minimise or remove the risk of cancer transmission from the transplantation process.

4.2 Solid Organ Tumours and Risk Assessment

Skin basal cell carcinomas and in situ epithelial carcinomas of many organs may be generally accepted as no-risk tumours. The only exception is high-grade in situ carcinoma of the breast, because this tumour can be understaged, particularly during organ procurement as frozen section may fail to detect foci of microinvasive carcinoma.

Renal cancer is the most common tumour detected during organ removal. Many literature reports suggest that I–II/IV Fuhrman grade renal cell carcinoma up to 4 cm (pT1a) shows a very low risk of cancer transmission [5].

In 2005 Buell et al. [10] reported to the Penn Tumour Registry that of 14 known cases of intentional transplant of kidneys with excised tumour (mean diameter 2.0 cm), there was no cancer transmission in the recipients at a mean of 69 months (range 14–200 months).

Transmission of kidney carcinoma has been described, although in some cases it was due to the use of organs from donors with high-stage tumours or an organ containing a tumour [11, 12]. In other cases, an incomplete histological report or the lack of molecular tests failed to demonstrate donor-recipient neoplastic transmission [13, 14].

The diagnosis of renal carcinoma during organ recruitment needs a team of pathologists with expertise in the field of kidney tumour pathology. The differential diagnosis between oncocytoma and chromophobe carcinoma can be extremely difficult on frozen section; oncocytoma is a benign kidney tumour, while chromophobe carcinoma can metastasize. Donors with kidney tumours more than 4 cm in size are generally not accepted for organ donation [5].

Thyroid Tumours Some very early types of thyroid carcinoma, such as encapsulated papillary or micropapillary carcinoma, may be considered a standard risk.

Prostate Cancer The incidence of prostate cancer increases with age, and the use of older donors includes an increased risk of identifying this cancer during organ

recruitment. PSA evaluation does not have a pivotal role because its values can be modified by ischaemia and manual procedures during catheterism.

There is no consensus on the procedure to follow for donors with prostate cancer. Some countries consider donors with prostate cancer an unacceptable risk for donation, whereas others (e.g. Italy [15]) consider donors with small intraprostatic low-grade (Gleason score ≤6) tumours a standard risk, while those with intraprostatic tumours with a Gleason score 7 are considered nonstandard risk. Histological examination of the entire prostate with tumour grading is time-consuming, and results may not be available before transplantation. A careful individual risk-benefit assessment must be undertaken. Donors with extraprostatic tumour extension or prostate cancer-related metastatic disease should be unequivocally excluded from the donation process.

Lung Carcinomas Lung cancer transmission from donor to recipients has been reported in the literature. In some cases the cancer (high-grade bronchogenic carcinoma) was identified at autopsy [16]. In others lung cancer transmissions were reported although the clinical history, biological behaviour [17] and the check of thoracic organs during organ recruitment [18] were not well described.

Generally, infiltrating non-small cell and small cell lung carcinomas are very aggressive tumours, and donors harbouring lung carcinomas should be considered an unacceptable risk for donation [5].

Gastrointestinal Adenocarcinoma (Stomach, Colon, Pancreas) Carcinomas of the gastrointestinal tract and pancreas tend to give rise to metastases. The use of organs from donors with pt2 pT3 tumours is generally unacceptable. In the case of pT1 tumours, the incidence of lymph node metastasis is very low, and a risk-benefit analysis is required.

Highly aggressive tumours include melanoma and choriocarcinoma. Melanoma is the most commonly transmitted tumour causing distant metastasis [19, 20] and death in organ recipients. The high rate of donor transmission of melanoma might be related to its biology, with regard to tumour dormancy, late recurrence, circulating tumour cells, circulating micrometastases or tumour cells lodged in the transplanted organs [20]. Melanoma cells can remain dormant at distant sites for decades (and possibly forever) in immunocompetent patients, only to be reactivated after transplantation into an immunosuppressed recipient.

These factors can explain donor-recipient melanoma transmission 16 years [21] and 32 years [22] after treatment and apparently cured melanoma in the donor. Donors dying from brain haemorrhage without a recognised cause need great attention during organ procurement. Knowledge of the clinical history and careful examination of the skin to identify scars or pigmented lesions can help discard an organ at high risk of melanoma transmission.

Choriocarcinoma must always be considered in the group of unacceptable risk. Any cerebral haemorrhage in a woman of childbearing age requires tests to rule out a diagnosis of choriocarcinoma metastasis [5].

Haematopoietic Malignancies Donors with leukaemia or lymphoma have to be considered in the group of unacceptable risk. In France donors with a history of

acute leukaemia can be considered for donation if the disease was completely cured at least 5–10 years before donor evaluation [5].

Tumours of the Central Nervous System CNS tumours carry a low risk of extraneural spread (0.4–2.3 %) [23]. The UNOS registry reported no cases of tumour transmission in a series of 397 donors with a history of CNS tumours who donated organs to 1,220 recipients [24]. Analysing data from 2000 to 2005, a subsequent paper by the same group reported 1 tumour transmission to 3 recipients in a series of 642 donors with a history of primary brain tumour including 175 organs from patients with glioblastoma multiforme. It should be kept in mind that during the same period 39,519 patients died on the waiting list [25, 26].

A retrospective analysis of UK Transplant Registry data showed that none of the 177 donors with primary intracranial malignancy transmitted the malignancy to the 448 recipients who received their organs. Many of these donors had high-grade tumours, including 23 grade IV gliomas (glioblastoma multiforme) and 9 with medulloblastoma who provided organs for 85 traceable recipients [27].

Nonetheless at least 30 cases of CNS tumour transmission are reported in the literature. Glioblastoma multiforme and medulloblastoma are the CNS malignancy tumours most often transmitted to the kidney and liver recipients [28, 29].

Although the risk of using organs from donors where there may be a low or even intermediate risk of disease transmission increasingly needs to be balanced against the likelihood of death on the transplant waiting list [30], safety in organ donation is paramount. The use of organs from donors with aggressive tumours should only be considered in cases of life-threatening emergency for the recipient.

If tumour transmission occurs, it is necessary to determine the imputability or certainty of donor tumour transmission. All the transplantation centres involved must be notified, and an appropriate evidence-based surveillance system is built and applied.

4.2.1 Organ Safety

The histological evaluation of donor liver and kidney biopsies is discussed in Section II-12 and Section III-22, respectively.

References

1. Nickkholgh A, Frey E, Krenzel C, Lauchart W, Flechtenmacher C, Schmidt J, Schemmer P. The need for vigilance in extended criteria donors with a past of malignancy: a case report and review of literature. Ann Tansplant. 2011;16:75–9.
2. Grossi PA, Fishman JA, AST Infectious Disease Community of Practice. Donor-derived infections in solid organ transplant recipients. Am J Transplant. 2009;9(Supp 4):S19–26.
3. Fishman JA, Greenwald MA, Grossi PA. Transmission of infection with human allograft: essential considerations in donor screening. Immunocompromised Hosts. 2012;55:720–7.
4. Fishman JA, Grossi PA. Donor-derived infection-the challenge for transplant safety. Nat Rev Nephrol. 2014;10:663–72.

5. Guide to the quality and safety of organs for transplantation. European Committee – partial agreement- on organ transplantation. 5th ed. 2013.
6. Kauffman HM, McBride MA, Cherikh WS, Spain PC, Marks WH, Roza AM. Transplant tumor registry: donor related malignancies. Transplantation. 2002;4:358.
7. Desai R, Collett D, Watson CJ, Johnson P, Evans T, Neuberger J. Cancer transmission from organ donors – unavoidable but low risk. Transplantation. 2012;94:1200–7.
8. Nalesnik MA, Woodle ES, Dimaio JM, Vasudev B, Teperman LW, Covington S, Taranto S, Gockerman JP, Shapiro R, Sharma V, Swinnen LJ, Yoshida A, Ison MG. Donor-transmitted malignancies in organ transplantation: assessment of clinical risk. Am J Transplant. 2011;11(6):1140–7.
9. Detry O, Bonnet P, Honorè P, Meurisse M, Jacquet N. What is the risk of transferral of an undetected neoplasm during organ transplantation? Tranplant Proc. 1997;29:2410–1.
10. Buell JF, Hanaway MJ, Thomas M, Munda R, Alloway RR, First MR, Woodle ES. Donor kidneys with small renal cell cancers: can they be transplanted? Transplant Proc. 2005;37(2):581–2.
11. Sack FU, Lange R, Mehmanesh H, Amman K, Schnabel P, Zimmermann R, Dengler T, Otto HF, Hagl S. Transferral of extrathoracic donor neoplasm by the cardiac allograft. J Heart Lung Transplant. 1997;16(3):298–301.
12. Ferreira GF, Azevedo de Oliveira R, Jorge LB, Nahas WC, Saldanha LB, Ianhez LE, Srougi M. Urothelial carcinoma transmission via kidney transplantation. Nephrol Dial Transplant. 2010;25:641–3.
13. Barrou B, Bitker MO, Delcourt A, Ourahma S, Richard F. Fate of renal tubulopapillary adenoma transmitted by an organ donor. Transplantation. 2001;72(3):540–1.
14. Llamas F, Gallego E, Salinas A, Virseda J, Pérez J, Ortega A, Nam SH, Gómez C. Sarcomatoid renal cell carcinoma in a renal transplant recipient. Transplant Proc. 2009;41(10):4422–4.
15. D'Errico-Grigioni A, Fiorentino M, Vasuri F, Corti B, Ridolfi L, Grigioni WF, Pathology Unit for organ safety of the F. Addarii Institute, Bologna, Bagni A, Pirini MG, Malvi D, Fabbrizio B, Caprara G, Alvaro N. Expanding the criteria of organ procurement from donors with prostate cancer: the application of the new Italian guidelines. Am J Transplant. 2010;10(8):1907–11.
16. Forbes GB, Goggin MJ, Dische FE, Saeed IT, Parsons V, Harding MJ, Bewick M, Rudge CT. Accidental transplantation of bronchial carcinoma from a cadaver donor to two recipients of renal allografts. J Clin Pathol. 1981;34(2):109–15.
17. Winter TC, Keller PR, Lee Jr FT, Pozniak MA. Donor-derived malignancy: transmission of small-cell lung cancer via renal transplantation. J Ultrasound Med. 2001;20(5):559–62.
18. Lipshutz GS, Baxter-Lowe LA, Nguyen T, Jones KD, Ascher NL, Feng S. Death from donor-transmitted malignancy despite emergency liver retransplantation. Liver Transpl. 2003;9(10):1102–7.
19. Zwald FO, Christenson LJ, Billingsley EM, Zeitouni NC, Ratner D, Bordeaux J, Patel MJ, Brown MD, Proby CM, Euvrard S, Otley CC, Stasko T, Melanoma Working Group of The International Transplant Skin Cancer Collaborative and Skin Care in Organ Transplant Patients, Europe. Melanoma in solid organ transplant recipients. Am J Transplant. 2010;10(5):1297–304.
20. Strauss DC, Thomas M. Transmission of donor melanoma by organ transplantation. Lancet Oncol. 2010;11:790–6.
21. MacKie RM, Reid R, Junor B. Fatal melanoma transferred in a donated kidney 16 years after melanoma surgery. N Engl J Med. 2003;348:567–8.
22. Bajai NS, Watt C, Hadjiliadis D, Gillespie C, Haas AR, Pochettino A, Mendez J, Sterman DH, Schuchter LM, Christie JD, Lee JC, Ahya VN. Donor transmission of malignant melanoma in a lung transplant recipient 32 years after curative resection. Transpl Int. 2010;23(7):e26–31.
23. Gandhi MJ, Strong DM. Donor derived malignancy following transplantation: a review. Cell Tissue Bank. 2007;8:267–86.

24. Kauffman HM, McBride MA, Cherikh WS, Spain PC, Delmonico FL. Transplant tumor registry: donors with central nervous system tumors. Transplantation. 2002;73(4):579–82.
25. Kauffman HM, Cherikh WS, McBride MA, Cheng Y, Hanto DW. Deceased donors with a past history of malignancies: an organ procurement and transplantation network/united network for organ sharing update. Transplantation. 2007;84(2):272–4.
26. Warrens AN, Birch R, Collett D, Daraktchiev M, Dark JH, Galea G, Gronow K, Neuberger J, Hilton D, Whittle IR, Watson CJ, Advisory Committee on the Safety of Blood, Tissues and Organs, UK. Advising potential recipients on the use of organs from donors with primary central nervous system tumors. Transplantation. 2012;93(4):348–53.
27. Watson CJ, Roberts R, Wright KA, Greenberg DC, Rous BA, Brown CH, Counter C, Collett D, Bradley JA. How safe is it to transplant organs from deceased donors with primary intracranial malignancy? an analysis of UK registry data. Am J Transplant. 2010;10(6):1437–44.
28. Jonas S, Bechstein WO, Lemmens HP, Neuhaus R, Thalmann U, Neuhaus P. Liver graft-transmitted glioblastoma multiforme. A case report and experience with 13 multiorgan donors suffering from primary cerebral neoplasia. Transpl Int. 1996;9:426–9.
29. Frank S, Muller J, Bonk C, Haroske G, Schackert HK, Schackert G. Transmission of glioblastoma multiforme through liver transplantation. Lancet. 1998;352:31.
30. Watson CJE, Bradley JA. Evaluating the risk of cancer transmission to optimize organ usage. Am J Transplant. 2011;11:1113–4.

Medical Disease After Abdominal Solid Organ Transplantation and the Risk of Solid and Hematologic Malignant Tumor After Transplantation

5

Maria Cristina Morelli

5.1 Summary

Solid organ transplantation is the treatment of choice for selected patients with end-stage organ insufficiency, improving long-term survival, enhancing quality of life, and proving cost benefit. Currently, the survival of patients after kidney and liver transplantation exceeds respectively 80 and 70 % after 5 years, associated in the majority of cases with a good quality of life [1]. While in the early postoperative period the main causes of morbidity and mortality are related to the primary organ dysfunction, surgical complications, or postoperative infection, in the long term, they are mainly related to the emergence of disorders linked to immunosuppressive therapy side effects or to primary disease recurrence [2].

Although rejection is an early event, usually in the first months posttransplantation, the majority of patients will require immunosuppression for life. The drugs most commonly used in induction and in maintenance are calcineurin inhibitors (cyclosporine and tacrolimus) in combination with steroids or mycophenolate mofetil.

Another class of immunosuppressants used in association with or in substitution of calcineurin inhibitors are mTOR inhibitors (rapamycin and everolimus) that, among others, have the ability to inhibit angiogenesis and tumor cell growth by blocking the action of mTOR, a protein involved in cell growth regulation and proliferation [3].

Monitoring immunosuppressive drug blood levels is a key point in the management of patients after solid organ transplantation in order to minimize the potential adverse effects; in addition, whenever a new medication is prescribed, it is necessary

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Table 5.1 Immunosuppressive drugs: main adverse effects

Adverse effect	Cyclosporine	Tacrolimus	Steroids	Aza	Mycophenolate mofetil	Sirolimus-everolimus
Arterial hypertension	+++	++	+++	–	–	+
Hyperglycemia	–	+	+++	–	–	–
Hyperlipidemia	++	+	++	–	–	+++
Impaired wound healing	–	–	+	+	+	++
Nephrotoxicity	+++	+++	–	–	–	Proteinuria
Neurotoxicity		++		–	–	–
Myelosuppression	+	+	–	+++	+++	++
Osteoporosis	+	+	+++	–	–	–
Oral ulcers						
Gastrointestinal	+	+	+	–	+++	++

to know its interactions with immunosuppressant drugs. Table 5.1 summarizes the main characteristics of immunosuppressants and the most frequent side effects.

A recent prospective study from the NIDDK Liver Transplantation Database showed that the probability of death after liver transplantation can be divided in three different phases: the first 6 months with a higher mortality (11 %) related to graft dysfunction and postoperative complications, the second between 6 months and 8 years with a relatively low and stable mortality rate (2–5 %/year), and a third after 8 years with an increasing mortality (6–7 %/year) in which the leading causes of late deaths are malignancy, cardiovascular disease, and renal failure. Likewise in the kidney transplant setting, cardiovascular disease (CVD) is the leading cause of death after transplantation and death with a functioning graft [4]. However, careful management of potentially modifiable risk factors such as metabolic syndrome, cardiovascular diseases, and renal insufficiency may improve long-term survival.

5.2 Metabolic Syndrome

The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) identified metabolic syndrome (MS) as a multiplex risk factor for cardiovascular disease (CVD). Clustering of metabolic abnormalities such as hypertension, dyslipidemia, elevated fasting blood glucose, and obesity is known as the metabolic syndrome (MS). Criteria of ATP III are shown in Table 5.1; diagnosis of MS can be made when at least three of five of the listed components are present. Abdominal obesity, recognized by increased waist circumference, is the first criterion listed. Also listed are raised triglycerides, reduced HDL cholesterol, elevated blood pressure, and raised plasma glucose. Explicit demonstration of insulin resistance is not required for diagnosis; however, most persons meeting ATP III criteria will be insulin resistant [5].

Table 5.2 ATPIII clinical identification of metabolic syndrome

Risk factor	Defining level
Abdominal obesity as waist circumference	
Men	>102 cm
Women	>88 cm
Triglycerides	≥150 mg/dl
HDL cholesterol	
Men	<40 mg/dl
Women	<50 mg/dl
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dl

MS is common among liver transplant recipients before and after transplantation. In the pre-transplant phase, the prevalence of MS can vary from 29 % in patients with cryptogenetic cirrhosis to 8 % in patients with end-stage liver disease caused by other etiologies [6]. Furthermore, the frequency of non-alcoholic fatty liver disease (NAFLD) as the indication for liver transplantation has been steadily increasing in recent years in all countries, and, in this population, obesity and diabetes are common features in patients awaiting liver transplant. In the kidney transplant setting, MS is a common condition after transplantation; the ALERT core study including 1,706 patients found that over 30 % of the recipients had MS criteria at entry [7]. After transplant many factors, primarily immunosuppression, contribute as a strong promoter of metabolic syndrome that develops in up to two-thirds of patients within the first five postoperative years. The most common metabolic side effects of immunosuppressive drugs are shown in Table 5.2. Other factors contribute to maintaining and raising the prevalence of metabolic syndrome after transplant, principally physical inactivity. Solid organ recipients are mostly sedentary, and most of them do not engage in work activity. Many studies revealed that transplant survivors had lower physical scores than the general population of the same age [8]. Calorie consumption, principally consisting of fat and carbohydrates, rises over the years after liver transplantation. Rising calorie intake combined with low physical activity contributes to the high prevalence of metabolic syndrome. Cirrhotic liver recipients lose lean mass in the pre-transplant period; the low levels of physical activity thereafter contribute to the reduction of lean mass and body water composition observed over the years. Other factors such as hepatitis C infection or methylprednisolone boluses are independent risk factors for the development of diabetes. As regards the function of the kidney graft, a recent study revealed that metabolic syndrome was associated with increased risk of graft failure [7].

5.3 Obesity

The WHO categorizes obesity according to BMI (overweight = BMI 25–29.9 kg/m^2, class I = BMI 30–34.9 kg/m^2, class II = BMI 35–39.9 kg/m^2, class III = BMI >40 kg/m^2). Abdominal obesity, typically manifesting as increased abdominal girth, is more metabolically active than peripheral adipose tissue; this feature has been associated with

a higher risk of cardiovascular disease than peripheral obesity [9]. Recent studies described that over one-third of patients with decompensated cirrhosis are obese. In addition, NAFLD-related cirrhosis as an indication for liver transplant has been shown to continue to increase over time. In a large study published in 2005, the 5-year mortality was significantly higher both in the severely and morbidly obese subjects ($P<0.05$), mostly as a result of adverse cardiovascular events concluding that morbid obesity should be considered a relative contraindication for liver transplantation [10]. Subsequent studies analyzed the confounding effect of ascites showing that correcting for ascites volume, 20 % of patients move into a lower BMI classification; these studies concluded that corrected BMI is not independently predictive of patient or graft survival and obesity "per se" should not be considered a contraindication for liver transplantation [11]. In the kidney transplant setting, almost 60 % of recipients are overweight at the time of transplantation, representing a 116 % increase from 1987. Indeed, in many transplant centers, a BMI of 35 kg/m^2 or greater is a common reason to exclude patients from transplantation. Despite this, the impact of obesity on patient and graft survival remains controversial [12].

5.4 Dyslipidemia

The prevalence of hypercholesterolemia after solid organ transplantation rises to 43 % and hypertriglyceridemia to 40 %, while in 10–12 % dyslipidemia is characterized by an increase of cholesterol and triglycerides. The etiology of posttransplant hyperlipidemia is multifactorial; the main causes are increased appetite, obesity, and high prevalence of de novo diabetes and chronic renal failure; these factors are associated with the lipid-increasing effect of immunosuppressive therapy. CsA, tacrolimus, and rapamycin enhance lipolysis and inhibit lipid storage and expression of lypogenic genes in adipose tissue, which may contribute to the development of dyslipidemia and insulin resistance associated with immunosuppressive therapy. Steroids increase the excretion and hepatic VLDL conversion to LDL. Dyslipidemia is a well-known risk factor for cardiovascular diseases and is associated with reduced graft and patient survival in transplant recipients [13].

5.5 Hypertension

Hypertension is defined as the development of arterial pressure values ≥140/90 in a previously normotensive patient. Systemic arterial hypertension is a major complication in organ transplantation, reaching a prevalence of between 60 and 90 % during treatment with calcineurin inhibitors 10 years after transplantation; 20 % of patients require treatment with more than one drug [14]. Therapy with calcineurin inhibitors and steroids is the main cause of hypertension; cyclosporine is associated with increased production of renin and angiotensin; both calcineurin inhibitors cause increased synthesis of vasoconstrictor factors such as endothelin and reduced secretion of vasodilators prostacyclin and nitric oxide. Steroids increase the activity of the renin-angiotensin

system and the vasoconstrictor response to norepinephrine and angiotensin II. In view of the risk of cardiovascular events in organ transplant patients, the blood pressure values recommended for the treatment of arterial hypertension are ≥130/80 mmHg and ≥125/75 mmHg in diabetic patients with proteinuria or renal insufficiency.

5.6 Diabetes

Cirrhotic patients frequently develop glucose intolerance and diabetes caused by insulin peripheral resistance, with reduced glycogen synthesis and impaired glucose oxidation [15]. Many patients will either remain diabetic or develop new-onset diabetes (NOD) after liver transplant.

Immunosuppressive therapy and HCV infection are the main risk factors related to post-liver transplant new-onset diabetes. Denervation of transplanted liver may contribute to the increase in insulin resistance. The incidence of preexisting diabetes as well as new-onset diabetes after renal transplantation (NODAT) varies from study to study and ranges from approximately 2–25 % with current immunosuppression, but with more diabetogenic immunosuppressive therapy, the incidence of diabetes may appear earlier after transplantation and can even rise to 46 % [16].

Corticosteroids decrease pancreatic beta-cell insulin production, increase gluconeogenesis, and decrease peripheral glucose utilization. In general, immunosuppression with calcineurin inhibitors leads to impaired glucose tolerance, and treatment with tacrolimus is associated with a higher risk of developing NODAT than treatment with cyclosporine [16]. Fasting glucose has a low sensitivity for diagnosing posttransplant diabetes mellitus (PTDM); therefore, the cutoff at 100 mg/dl for impaired fasting glucose seems more appropriate than 110 mg/dl. At present, the oral glucose tolerance test (OGTT) is considered the gold standard for diagnosing PTDM [17]. Regular monitoring of fasting blood glucose and OGTT, at least every 3 months, is strongly advised. Glycosylated hemoglobin assay (HbA1c) should be performed periodically after the third posttransplant month; HbA1c 5.7–6.4 % or higher indicates the need to follow up with a recognized diagnostic test.

5.7 Cardiovascular Disease (CVD)

Although renal transplantation substantially reduces cardiovascular risk, CVD remains the most important cause of morbidity and mortality. CVDs are the third most common late cause of death also in liver transplantation, accounting for 12–21 % of deaths; this may be an underestimation since some deaths characterized as “unknown” include sudden cardiac deaths. Detection and early treatment of risk factors of cardiovascular disease may impact long-term posttransplant survival. A recent meta-analysis showed that the 10-year risk of developing CV events among the post-OLT recipients was 13.6 % with a 64 % greater risk of experiencing CV events than controls. Liver recipients with metabolic syndrome were approximately four times more likely to have a CV event [18].

5.8 Recommendations for Management of Metabolic Syndrome and Cardiovascular Diseases

5.8.1 Lifestyle Control

For many obese patients, sustained weight loss and exercise are unfortunately difficult to achieve, particularly in the setting of liver transplant recipients. Many patients remain sedentary after transplant, only a quarter are physically active after transplant, and up to two-thirds were found to have a higher than recommended energy intake. A single randomized trial evaluated the effects of exercise and dietary counseling after transplantation. An improvement in cardiorespiratory fitness and quality of life was reported in the intervention group, but no changes were noted in body composition or muscle strength. The primary aim of counseling should be to prevent weight gain rather than the treatment of the metabolic syndrome when it has already occurred [19, 20, 21].

5.8.2 Immunosuppression Management

Modifying immunosuppression can improve blood pressure and glycemic and lipid profile. When possible, achieving steroid-free regimes should be the primary intervention in order to reduce the prevalence of diabetes, hypertension, and hypercholesterolemia. Only a minority of patients require maintenance corticosteroids, which can and should be discontinued well before the end of the first postoperative year. Compared to cyclosporine, tacrolimus is associated with a decreased risk of hypertension but is associated with an increased risk of diabetes. Introducing mycophenolate mofetil (MMF) with low doses of calcineurin inhibitors ameliorates hypertension, diabetes, and renal function with a low risk of rejection. Conversion from CNI to mTOR-based immunosuppression can reduce hypertension and diabetes but is associated with onset or worsening of dyslipidemia. Mainly, there is no ideal immunosuppressive regimen in patients with metabolic syndrome, but the modulation and the use of a combination of drugs at low dose is probably the best way to mitigate the side effects of immunosuppressive therapy.

5.9 Pharmacotherapy

5.9.1 Hypertension

Calcium channel blockers (CCBs) (nifedipine, nicardipine, and amlodipine) are usually the first-line antihypertensive agents in solid organ transplantation, whereas diltiazem and verapamil are difficult to manage for interaction with calcineurin inhibitors. CCBs lower BP independent of age, gender, ethnicity, and salt intake. This class induces vasodilation and counteracts the vasoconstrictive effects of CNIs [22]. The activation of the renin-angiotensin-aldosterone system (RAAS) plays an important role in the late period after transplantation; therefore,

angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers are suggested especially in the late period of transplant or early in the presence of proteinuria or in combination with calcium channel blockers. RAAS block is an important factor in HTN treatment in the renal transplant patient, particularly those with diabetes and proteinuria [23]. Regarding beta-blockers, a recent comparative study between nifedipine and carvedilol showed no difference between the two drugs but only 20 % of patients achieved effective blood pressure control with monotherapy, with a higher rate of response of nifedipine and ACE inhibitor combination versus a beta-blocker and ACE inhibitor.

5.9.2 Diabetes

There are no comparative studies on the effectiveness of different oral hypoglycemic agents after liver transplantation, and the choice should be focused on the individual clinical characteristics. Metformin can be used but is contraindicated in patients with creatinemia >1.5 mg/dL in males and >1:25 mg/dl in females due to the risk of developing lactic acidosis.

The glitazone side effects such as weight gain, edema, and anemia make them difficult to use in liver transplant recipients, and they are contraindicated in liver failure. If oral hypoglycemic agents are contraindicated or ineffective to maintain fasting blood glucose <120 mg/dL or glycosylated hemoglobin <7 %, then insulin treatment should be started.

5.9.3 Dyslipidemia

If an improvement in the lipid profile is not obtained after 6 months of a low-cholesterol diet and increasing aerobic physical activity, then hypolipidemic agents are required. Therapy with statins is particularly problematic due to the risk of interaction with calcineurin inhibitors and mTOR inhibitors. The risk of drug interactions is diminished with pravastatin and fluvastatin, which are only partially metabolized by human cytochrome P450 3A. Treatment with statins should be started with low doses and preferentially with those at a lower risk of interaction with immunosuppressive therapy. Monitoring of CPK, AST, and ALT over time is required. Ezetimibe has recently been shown to be effective and safe in patients undergoing liver transplantation. Fibrates are contraindicated in renal failure and in combination with statins and calcineurin inhibitors [24].

5.10 Renal Insufficiency in Nonrenal Organ Transplantation

Chronic renal failure is one of the most frequent complications of nonrenal organ transplantation. Renal insufficiency/failure occurred in over 68 % of patients in the posttransplant period and was shown to be an important risk factor for late death.

The 5-year risk of chronic renal failure (defined as a glomerular filtration rate of 29 ml per minute per 1.73 m^2 of body surface area or less) varied according to the type of organ transplanted and reaches 18 % in liver transplant recipients; the prevalence of end-stage renal failure which requires dialysis or kidney transplantation in this population is about 4 %. Renal failure has a high impact on the outcome of transplant. In particular, the onset of end-stage renal disease requiring hemodialysis in the liver recipient leads to a marked reduction in survival [25]. Older age, pre-LT RI, pre- and post-LT diabetes, and ALD are strongly associated with renal insufficiency after liver transplantation and should be identified in liver recipients who may benefit from combined liver kidney transplantation. Although the development of chronic renal failure is a late event in the natural history of liver transplant patients, it has already been shown that 25–50 % of kidney function is lost in the first year posttransplant, during the period of higher doses of immunosuppressive drugs. In particular, the reduction of renal function is greater in the first 3 months posttransplant, followed by a continuous decline (about 5 % per year), demonstrating the progression of renal damage despite the reduction of the immunosuppressive strain. Posttransplant renal failure may be manifested by features of acute renal failure, which occurs in the immediate postoperative period, or chronic renal disease, which in the majority of cases develops between 5 and 10 years after transplantation.

Acute renal failure is characterized in about half the cases by acute tubular necrosis. The most common causes are renal ischemia related to episodes of hypovolemia or sepsis in the peri- and postoperative period and the use of calcineurin inhibitors. Acute nephrotoxicity from calcineurin inhibitors is a reversible and dose-independent phenomenon caused principally by the increased synthesis or release of vasoconstrictor factors such as endothelin and reduced synthesis or release of renal vasodilator factors such as prostacyclin [26]. As regards chronic renal failure, the most important pathogenic factor is the nephrotoxicity of calcineurin inhibitors. The protracted vasoconstriction induced by these drugs, together with their direct toxic effects, leads to irreversible histological changes such as thickening of the arteriolar walls with narrowing and obstruction of the lumen, glomerulosclerosis, tubular atrophy, and interstitial fibrosis. Chronic nephrotoxicity from calcineurin inhibitors is therefore a phenomenon not dose dependent and not totally reversible.

5.10.1 Prevention and Treatment

In recipients at risk of developing acute renal failure, such as those with hepatorenal syndrome or in critically ill patients with high MELD score, the delay of calcineurin inhibitor introduction may be advised. Pilot studies have shown that immunosuppressive induction with anti-interleukin-2 receptor antibodies (basiliximab and daclizumab) to delay CNI administration may be an option [27].

In patients at high risk of chronic renal failure after transplantation, nephroprotective strategies should be adopted as early as possible. Primarily, the control of those factors which may contribute to kidney damage, such as hyperglycemia, hypertension, or HCV infection, is essential. Changes of immunosuppression range from CNI reduction to CNI-free regimens. Combined mycophenolate mofetil (MMF) and minimal dose CNI treatment leads to an improvement in renal function without an increased risk of rejection [28, 29]. As regards regimens CNI-free, the few published prospective randomized studies investigated the mTOR inhibitor-based immunosuppression. In a recent prospective study including 21 patients with chronic renal dysfunction, CNI discontinuation was feasible in 95.2 % of patients who were converted to everolimus. Kidney function significantly improved at day 30, but failed to show an advantage 3 and 6 months post-conversion [30].

5.11 Risk of Solid and Hematologic Malignant Tumors After Transplantation

The first important information on malignancies after solid organ transplantation comes from the Israel Penn International Transplant Tumor Registry published in the New England Journal of Medicine in 1990; from the analysis of 5,250 tumors that occurred in 4,993 patients, evidence has accumulated that organ transplantations are complicated by an increased incidence of certain types of tumor [31]. De novo solid malignancies are the second leading cause of late mortality in patients undergoing solid organ transplantation, accounting for over 25 % of deaths in patients surviving more than 3 years after transplantation [32, 33]. The risk of developing de novo malignancies in transplant patients is generally two to three times higher than that of the general population. Nonmelanoma skin cancer is the most frequent tumor detected after solid organ transplantation. Skin cancers usually have a histological distribution different from that of the non-transplanted population with a prevalence of squamous cell carcinomas compared to basal; the prevalence of the former is 40–250 times higher than that of the general population. The increased risk of de novo malignancy is particularly relevant for cancers related to viral infections, such as non-Hodgkin lymphomas (posttransplant lymphoproliferative disease (PTLD)), Kaposi's sarcoma, and cervical cancer. Non-Hodgkin lymphoma is the second most common cancer after transplantation; the lack of immune control against Epstein-Barr virus (EBV) infection is the principal cause of PTLD, especially for children who experience primary EBV infection after transplantation. The 5-year cumulative incidence ranges from 0.09 to 3.28 % across categories of sex, age, and transplanted organs; in particular, the incidence was high among the youngest patients for all solid organ recipients. Lung cancer is the next most common malignancy among heart and lung recipients, and it seems related to smoking as a factor implicated in end-stage heart and

lung disease. In lung recipients, cancer is most often diagnosed in the remaining native lung. Like lung cancer in lung recipients, kidney cancer is most common in kidney recipients and frequently arises in the native kidneys in association with acquired polycystic kidney disease [34]. The cumulative incidence of colorectal cancer was also high after transplantation, particularly for older recipients aged >50 years.

There are no data of an increased incidence compared to the reference population regarding prostate and breast cancer. It should be noted that some types of cancer are associated specifically with the etiology of the disease that led to transplantation. In particular, there is a significant increase in the risk of colorectal cancer in patients undergoing liver transplantation for primary sclerosing cholangitis associated with ulcerative colitis. Another group at high risk of de novo malignancy is that of patients transplanted for alcoholic cirrhosis in which there is a high prevalence of oropharynx and lung cancers. The frequent association of alcohol abuse with smoking reflects what has already been known in non-transplanted populations in terms of cancer risk.

5.11.1 Recommendations

Optimization of immunosuppressive therapy regimens avoiding overdoses or too strong immunosuppression is the first intervention strategy, mainly in long-term care. The use of mTOR inhibitors associated with a lower incidence of skin cancers is already confirmed in patients with renal transplantation. Early surveillance of viral load in serologically EBV- or HHV-8-negative recipients who received organs from donors EBV or HHV-8 positive is strongly advised. Lifestyle intervention with smoking and alcohol intake suspension is recommended, as is reducing exposure to sunlight without protection. Regarding cancer prevention, Table 5.3 reports the main screening recommendations for organ transplant population.

In addition, ultrasound screening may be cost-effective for high-risk subgroups of kidney recipients, such as those with acquired polycystic kidney disease, a family history of kidney cancer, or tobacco use [35].

Table 5.3 Cancer screening recommendation for organ transplant population

Skin cancer	Annual dermatologist control
Breast cancer	Annual mammography in women aged 40 years or older
Colon cancer	Colonoscopy every 5 years in people aged >50 years
	Annual colonoscopy in PSC recipients
Prostatic cancer	Annual urological control
Uterine cervix cancer	PAP test every 2 years
Recipient transplanted for alcoholic cirrhosis	Annual otolaryngologist control and gastroesophageal endoscopy

References

1. Pfitzmann R, Nüssler N, Hippler-Benscheidt M, Neuhaus R, Neuhaus P. Long-term results after liver transplantation. Transpl Int. 2008;21(3):234–46.
2. Westbrook RH, Yeoman AD, Agarwal K, Aluvihare V, Mieli- Vergani G, Dhawan A, et al. An evaluation of mortality in adults and children who have survived in excess of 5 and 10 years since liver transplantation [abstract]. Liver Transpl. 2009;15 suppl 7:S101.
3. Meier-Kriesche HU, et al. Immunosuppression: evolution in practice and trends, 1994–2004. Am J Transplant. 2006;6:1111–31.
4. Kasiske B, Guijarro C, Massy Z, Wiederkehr M, Ma J. Cardiovascular disease after renal transplantation. J Am Soc Nephrol. 1996;7:158–65.
5. Grundy S, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112:2735–52.
6. Tellez-Avila F, Sanchez-Avila F, Garcia-Saenz-de-Socolia M, Chavez-Tapia NC, Granco-Gusman AM, Lopez-Arce G, et al. Prevalence of metabolic syndrome, obesity and diabetes type 2 in cryptogenic cirrhosis. World J Gastroenterol. 2008;14:4771–5.
7. Soveri I, Abedini S, Holdaas H, Jardine A, Eriksson N, Fellström B. Graft loss risk in renal transplant recipients with metabolic syndrome: subgroup analyses of the ALERT trial. J Nephrol. 2012;25(02):245–54.
8. Anastacio LR, Diniz KG, Ribeiro HS, Ferreira LG, Lima AS, Correia MI, Vilela EG. Prospective evaluation of metabolic syndrome and its components among long-term liver recipients. Liver Int. 2014;11:5–8.
9. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L, INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937–52.
10. Poonawala A, Nair S, Thuluvath P. Prevalence of obesity and diabetes in patients with cryptogenic cirrhosis: a case-control study. Hepatology. 2000;32:689–92.
11. Leonarda J, Heimbachb JK, Malinchocc M, Watta K, Charlton M. The impact of obesity on long-term outcomes in liver transplant recipients—results of the NIDDK liver transplant database. Am J Transplant. 2008;8:667–72.
12. Hoogeveen EK, Aalten J, Rothman KJ, et al. Effect of obesity on the outcome of kidney transplantation: a 20-year follow-up. Transplantation. 2011;91:869–74.
13. Massy ZA. Hyperlipidemia and cardiovascular disease after organ transplantation. Transplantation. 2001;72:S13–5.
14. Stegall MD, Everson G, Schroter G, et al. Metabolic complications after liver transplantation. Diabetes, hypercholesterolaemia, hypertension, and obesity. Transplantation. 1995;60:1057.
15. Duclos A, Flachner IM, Faiman C, et al. Post-transplant diabetes mellitus: risk reduction strategies in the elderly. Drugs Aging. 2006;23:781–93.
16. Heisel O, et al. New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. Am J Transplant. 2004;4:583–95.
17. Sharif A, Moore RH, Baboolal K. The use of oral glucose tolerance tests to risk stratify for new-onset diabetes after transplantation: an underdiagnosed phenomenon. Transplantation. 2006;82:1667–72.
18. Madhwal R, Atreja A, Albeldawdi M, Lopez R, Post A, Costa MA. Is liver transplantation a risk factor for cardiovascular disease? a meta-analysis of observational studies. Liver Transpl. 2012;18:1140–6.
19. Beyer N, Aadahl M, Strange B, Kirkegaard P, Hansen BA, Mohr T, Kjaer M. Improved physical performance after orthotopic liver transplantation. Liver Transpl Surg. 1999;5:301–9.
20. Krasnoff JB, Vintro AQ, Ascher NL, Bass NM, Paul SM, Dodd MJ, Painter PL. A randomized trial of exercise and dietary counseling after liver transplantation. Am J Transplant. 2006;6:1896–905.

21. Painter P, Krasnoff J, Paul SM, Ascher NL. Physical activity and health-related quality of life in liver transplant recipients. Liver Transpl. 2001;7:213–9.
22. Sennesael JJ, Lamote JG, Violet I, Tasse S, Verbeelen DL. Divergent effects of calcium channel and angiotensin converting enzyme block- ade on glomerulotubular function in cyclosporine-treated renal allograft recipients. Am J Kidney Dis. 1996;27(5):701–8.
23. Cross NB, Webster AC, Masson P, O'connell PJ, Craig JC. Antihypertensives for kidney transplant recipients: systematic review and meta-analysis of randomized controlled trials. Transplantation. 2009;88(1):7–18.
24. Grazi IF, et al. Statins and solid organ transplantation. Curr Pharm Des. 2006;12:4771–83.
25. Ojo AO, Held PJ, Port KF, Robert A, Wolfe MS, Leichtman AB, Young EW, Arndorfer J, Christensen L, Merion RM. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med. 2003;349:931–40.
26. Textor SC, Burnett Jr JC, Romero JC, Canzanello VJ, Taler SJ, Wiesner R, Porayko M, Krom R, Gores G, Hay E. Urinary endothelin and renal vasoconstriction with cyclosporine or FK506 after liver transplantation. Kidney Int. 1995;47(5):1426–33.
27. Eckhoff DE, McGuire B, Sellers M, Contreras J, Frenette L, Young C, Hudson S, Bynon JS. The safety and efficacy of a two-dose daclizumab (zenapax) induction therapy in liver transplant recipients. Transplantation. 2000;69(9):1867–72.
28. Kornberg A, Kupper B, Hommann M, Scheele J. Introduction of MMF in conjunction with stepwise reduction of calcineurin inhibitor in stable liver transplant patients with renal dysfunction. Int Immunopharmacol. 2005;5:141–6.
29. Biselli M, Vitale G, Gramenzi A, et al. Two year mycophenolate mofetil plus low-dose calcineurin inhibitor for renal dysfunction after liver transplant. Clin Transplant. 2009;23:191–8.
30. Castroagudin JF, Molina E, Romero R, et al. Improvement of renal function after the switch from a calcineurin inhibitor to everolimus in liver transplant recipients with chronic renal dysfunction. Liver Transpl. 2009;15:1792–7.
31. Penn I. Cancers complicating organ transplantation. N Engl J Med. 1990;323(25):1767–9.
32. Pruthi J, Medkiff KA, Esrason KT, Donovan JA, Yoshida EM, Erb SR, Steinbrecher UP, Fong TL. Analysis of causes of death in liver transplant recipients who survived more than 3 years. Liver Transpl. 2001;7:811.
33. Haagsma EB, Hagens VE, Schaapveld M, van den Berg AP, de Vries EG, Klompmaker IJ, et al. Increased cancer risk after liver transplantation: a population-based study. J Hepatol. 2001;34:84–91.
34. Goh A, Vathsala A. Native renal cysts and dialysis duration are risk factors for renal cell carcinoma in renal transplant recipients. Am J Transplant. 2011;11:86–92.
35. Herrero JI. De novo malignancies following liver transplantation: impact and recommendations. Liver Transpl. 2009;15:S90–4.

Part II

Liver Transplantation

Indications for Liver Transplantation

6

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The list of indications for liver transplantation (LT) includes irreversible causes of end-stage liver disease which are curable by the procedure. More than a decade ago, the American Association for the Study of the Liver Disease (AASLD) established minimal listing criteria for patients with end-stage liver disease. To qualify for waiting list, the 1 year expected survival should be <90 % without LT. Liver transplantation should lead to prolonged survival and/or an improved quality of life [10]. Indications can be segregated into two classes: (1) acute conditions leading to a rapid and irreversible liver failure and (2) chronic diseases that can lead to liver failure and/or complications of end-stage liver disease. In the present introduction, causes of acute liver failure were discussed, whereas in the following chapters, each indication for LT was reported and analyzed.

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6.1 Acute Liver Failure

Acute liver failure (ALF or fulminant hepatic failure) is characterized by the rapid progress of encephalopathy, jaundice, and coagulopathy. It accounts for 5–6 % of all patients undergoing liver transplantation [1]. Acetaminophen toxicity is the leading cause of ALF in Western countries, and hepatitis A, E, and B and seronegative hepatitis represent other frequent etiological factors. Patients who meet the King's College criteria (Table 6.1) for urgent transplantation provide a very small window for action, and they need to undergo transplantation, as soon as possible. There is a 100 % percent mortality if these selected patients do not undergo transplantation, and this is either due to liver failure per se or because of sepsis and multiorgan failure [2]. A meta-analysis published in 2003 indicated that the specificity of the King's College criteria in predicting mortality exceeded 90 %, with a sensitivity of 69 % [3].

Patients with subacute failure have a poor outcome with almost universal mortality if not transplanted. Timely referral is important in these patients because in the absence of transplantation, death may occur from sepsis and cerebral edema. Other scoring systems for listing a patient for urgent liver transplantation include Clichy criteria for acute viral hepatitis and Wilson's prognostic index/revised Wilson's prognostic index (Table 6.2) [4–7].

6.1.1 Indications for Transplantation

6.1.1.1 Acute Liver Failure

Hepatitis A, acetaminophen, autoimmune hepatitis
Hepatitis B
Hepatitis C, cryptogenic
Drugs, hepatitis D
Wilson's disease, Budd-Chiari syndrome
Hepatic trauma
Fatty infiltration—acute fatty liver of pregnancy, Reye's syndrome

Table 6.1 King's College criteria

Acetaminophen-induced ALF	Nonacetaminophen ALF
Arterial pH <7.3 irrespective of grade of encephalopathy or	INR >6.5 (PT >100 s), irrespective of grade of encephalopathy
PT >100 s	Or any 3 of the following:
Serum creatinine >3.4 mg/dL	INR >3.5 (PT >50 s)
Stage 3 or 4 encephalopathy	Age <11 or >40 years
	Serum bilirubin >18 mg/dL
	Time from onset of jaundice to coma development >7 days
	Drug toxicity, regardless of whether it was the cause of the acute liver failure

Table 6.2 Prognostic index in fulminant Wilson's hepatitis (WPI)

Score	0	1	2	3	4
Serum bilirubin (mg/dL)	<5.8	5.9–8.8	8.9–11.7	11.8–17.5	>17.5
Serum aspartate transaminase (IU/L)	<100	100–150	151–200	201–300	>300
Prothrombin time prolongation (INR)	<1.3	1.6–1.6	1.6–1.9	1.9–2.4	>2.4

Patients with a WPI score ≥7 need urgent liver transplantation

6.1.1.2 Cirrhosis from Chronic Liver Disease

Chronic hepatitis B virus infection
Chronic hepatitis C virus infection
Alcoholic liver disease
Cryptogenic liver disease
Autoimmune hepatitis
Nonalcoholic fatty liver disease

6.1.1.3 Liver Tumors

Hepatocellular carcinoma
Carcinoid tumor
Islet cell tumor
Epithelioid hemangioendothelioma
Cholangiocarcinoma

6.1.1.4 Metabolic Liver Disorders

Wilson's disease
Hereditary hemochromatosis
Alpha 1-antitrypsin deficiency
Glycogen storage disease
Cystic fibrosis
Glycogen storage disease I and IV
Crigler-Najjar syndrome
Galactosemia
Type 1 hyperoxaluria
Familial homozygous hypercholesterolemia
Hemophilia A and B

6.1.1.5 Liver Vascular Diseases

Budd-Chiari syndrome
Veno-occlusive disease

6.1.1.6 Cholestatic Liver Diseases

Primary sclerosing cholangitis
Primary biliary cirrhosis
Secondary biliary cirrhosis
Alagille syndrome
Biliary atresia
Byler's disease

6.1.1.7 Miscellaneous

Caroli's disease
Amyloidosis
Polycystic liver disease
Nodular regenerative hyperplasia
Severe graft-versus-host disease
Sarcoidosis
Variant syndromes requiring liver transplantation
Intractable ascites
Diuretic resistant, nonresponsive to TIPS, or TIPS contraindicated
Hepatopulmonary syndrome
Shunt fraction >8 %, pulmonary vascular dilatation
Chronic hepatic encephalopathy
Persistent and intractable pruritus

6.1.2 Possible Contraindications to Liver Transplantation

Age >65 years.
Severe malnutrition (BMI <19–20 at time of transplantation). Malnutrition may be reversible with vigorous therapy.
Other organ failure.
Previous upper abdominal surgery.
Poor functional status.
Poor medical compliance.
Severe cardiopulmonary disease.
Irreversible cerebral injury.
Sepsis or active infection.
HIV/AIDS.
Extrahepatic malignancy (the disease-free period >2–5 years, depending on malignancy type).
Extensive portal and mesenteric vein thromboses.
Active alcohol or drug usage (abstinent <3–6 months).
Psychosocial issues—inability to understand the procedure.
Severe psychological disorders which will prevent medical compliance.
Lack of social support.

6.2 Viral Chronic Hepatitis

Ranka Vukotic, and Pietro Andreone

Chronic hepatitis B virus (HBV)-related and hepatitis C virus (HCV)-related end-stage liver diseases lead to liver transplantation (LT). Nowadays, the availability of hepatitis B virus immunoglobulin (HBIG) and nucleos(t)ide analogues (NUCs) has allowed successful outcomes of most LTs for HBV-related end-stage liver disease. As far as HCV is concerned, post-LT recurrence is practically certain and has represented a great challenge in the IFN-based treatment era, which will probably soon be replaced by IFN-sparing regimens, radically changing the management and the long-term outcome of LT for HCV-related disease.

6.2.1 HBV and Liver Transplantation

In the last few years, in Western countries, the application of efficacious antiviral therapy has changed both the rate of transplants and the main indication for HBV-related LT which has become hepatocellular carcinoma rather than a very end-stage liver disease. Moreover, these therapeutic opportunities have allowed a significantly longer and better survival of the patients transplanted for HBV, since NUCs combined with HBIG protect the graft almost universally from HBV recurrence [8, 9]. At present, the 5-year survival rates in patients undergoing LT for HBV-related cirrhosis are around 80 %.

However, the patients transplanted for HBV are regularly monitored for HBV DNA and HBsAg in order to rapidly identify a possible, although extremely rare, recurrent HBV infection. If this occurs, liver histology is indicated to assess and monitor the presence and the stage of fibrosis. Currently, a severe fibrosing cholestatic onset is almost anecdotic and can be revealed by poorly expressed inflammatory features, high intrahepatic HBV DNA, presence of ballooning, and cholestasis [10]. A high level of HBV DNA at the time of LT is the most important index of the risk of hepatitis B recurrence [11], so the achievement of HBV DNA suppression is the goal in end-stage patients awaiting LT.

Lamivudine was the first nucleoside analogue approved for hepatitis B, offering epochal results in obtaining suppression of HBV viremia and ameliorating liver function, but hampered by a high resistance rate due to development of mutations in the YMDD locus of the polymerase gene (10–20 % at 1 year, around 60 % at 4 years). Adefovir showed satisfactory results in treating patients with lamivudine resistance but presented high rates of long-term treatment-related resistance and an important nephrotoxicity issue [12]. Fortunately, new oral antiviral agents (tenofovir and entecavir) were subsequently developed, showing greater efficacy, in terms of HBV DNA clearance and liver function improvement, and guaranteeing a higher resistance barrier [13, 14]. Of note, these agents require strict monitoring of renal function to exclude, as early as possible, any tubular injury which can provoke severe hypophosphoremia and/or lactic acidosis [15].

6.2.1.1 Post-LT Hepatitis B Prophylaxis

HBIG is burdened by its high costs and a suboptimal effectiveness in monotherapy. It has been demonstrated that beginning parenteral HBIG immediately after LT leads to a significant reduction in graft infection and an increase in 3-year survival [16]. Nevertheless, despite several solid immunological-acting pathways, HBIG should not be used in monotherapy since high rates of post-LT HBV recurrence have been reported in LT recipients treated with this strategy. On the other hand, lamivudine post-LT monotherapy leads to high rates of HBV recurrence, while the combination of HBIG and lamivudine has been seen to be an effective recurrence prophylaxis [17, 18]. Those patients who develop resistance to lamivudine during combined HBIG and lamivudine prophylaxis are commonly treated with tenofovir monotherapy rather than adefovir add-on, especially in view of the cost-effectiveness and safety issues. In short, if appropriately combined with available NUCs, HBIG use can be optimized in terms of costs and feasibility by administering lower doses and preferring intramuscular injections to intravenous regimens. As regards dose minimization or even prophylactic treatment withdrawal, this was prospectively explored in a study in which a gradual HBIG withdrawal was followed by antiviral discontinuation in patients not showing covalently closed circular HBV DNA in liver biopsy. At follow-up, more than 80 % of patients did not present HBV recurrence [19]. Recently, the efficacy of monotherapy with entecavir was examined in 80 subjects who underwent LT for HBV, showing cumulative rates of HBsAg clearance of 91 % after 2 years and almost 100 % of HBV DNA undetectable patients [20]. This approach might be taken into account in subjects who at the time of LT are HBeAg negative/HBV DNA undetectable. The vaccination strategy should be adopted since so far the studies including the use of adjuvanted vaccines are not encouraging [21]. Finally, the complete withdrawal of post-LT HBV prophylaxis in selected low-risk populations can be hypothesized, but is still debated and insufficiently explored.

6.2.1.2 Post-LT Hepatitis B Recurrence

A real de novo HBV infection post-LT is an extremely rare event. On the other hand, suboptimal adherence to the pharmacological prophylaxis and resistance phenomena might lead to HBsAg reappearance after an initial fade-out. If serum HBV DNA also becomes detectable, the antiviral therapy should be promptly started so as to avoid chronic liver injury development and progression, to prevent graft loss, and to reduce complication onset and mortality. The possible strategies should be tailored according to the virological and clinical characteristics of HBV recurrence. In particular, entecavir or tenofovir is used as an effective option if HBIG resistance occurs, taking into consideration that lamivudine resistance should be treated with tenofovir rather than entecavir, which might develop resistance as well. On the other hand, starting tenofovir should be evaluated carefully in patients with renal failure, especially considering proteinuria and previous tubular damage. When necessary, although there are no extensive data to support this approach, the combination of these two analogues can be considered if complex resistance features emerge [22].

6.2.1.3 De Novo HBV Infection Prophylaxis in Recipients of Anti-HBc-Positive Donor Livers

Over the years, the expansion of the donor pool has been proposed to allow greater LT access, and this was extended to HBsAg-negative/hepatitis B core antigen-antibody (anti-HBc)-positive donors, ideally allocating these organs to already HBsAg-positive liver recipients, previously undergoing immunoprophylactic HBV regimen [23]. In fact, an extensive review of the studies using livers from anti-HBc-positive donors in HBsAg-negative recipients revealed the probability of de novo HBV infection in recipients who did not receive immunoprophylaxis in anti-HBc-/anti-HBs-patients, of 15 % in anti-HBs+ and/or anti-HBc+, and of less than 2 % in anti-HBc–/anti-HBs+ recipients. In anti-HBc+ graft recipients, HBIG is not necessary, while lamivudine monotherapy seems to ensure satisfactory low rates of graft infection (<3 %).

In conclusion, the combination of antiviral drugs and low-dose HBIG can effectively prevent HBV recurrence in almost all LT recipients. HBIG discontinuation can be taken into consideration, maintaining the NUCs in those patients who do not have apparent risk factors for recurrence and who had low or undetectable HBV DNA levels before LT. These prophylactic and therapeutic approaches have drastically modified the natural history and the prognosis of both pre-LT and post-LT HBV-related settings.

6.2.1.4 HCV and Liver Transplantation

Hepatitis C virus (HCV) infection can lead to cirrhosis and its complications and represents the main indication for LT, at least in the Western countries [24]. Unfortunately, in HCV RNA-positive patients, the recurrence of HCV infection after LT is universal [25, 26] and may lead to cirrhosis in approximately 30 % of recipients after 5 years [27]. The severity of the infection is unpredictable and often associated with additional clinical and histological features (e.g., cholestasis, de novo autoimmunity, coinfections), determining a more rapid progression versus advanced illness and possible graft loss. LT patients who undergo antiviral therapy have been shown to have a longer survival, better histological and hemodynamic long-term features, and a lower rate of decompensation [28–31], especially when a sustained virological response (SVR) is achieved. However, dual antiviral therapy with pegylated interferon (PegIFN) and ribavirin (RBV) seems to be poorly effective in this population [32]. Direct-acting antiviral agents (DAA) such as protease inhibitors (PI) have been seen to ameliorate the rate of SVR in pre-LT genotype 1 patients, both treatment naive and experienced [33, 34]. Recently, several experiences have been reported regarding the use of the new antiviral agents in LT recipients, focusing not only on the likelihood of achieving higher SVR rates with the new antiviral regimens but also on the complex issue of immunosuppressant drug handling, drug interactions, and increase of renal and hematopoietic toxicity [35–38]. These data confirmed that, also in post-LT hepatitis C settings, similar SVR rates to those of non-LT patients can be achieved by triple regimens with PI, peginterferon, and ribavirin. Moreover, satisfactory SVR rates have been obtained despite several adverse events such as anemia, neutropenia, rash, and renal failure. The worldwide growing experience with the use of telaprevir and boceprevir in LT recipients with HCV recurrence has significantly

helped clinicians in the use of new DAAs, especially in awareness on the drug-drug interaction issue and the possible induction of plasma cell hepatitis during triple IFN-based regimens, sometimes with acute rejection-like onset resulting in graft loss or in fatal outcome [39–41]. On the other hand, it is possible that the high costs of oncoming potent IFN-free regimens will be prohibitive for many developing countries which will continue to rely on PIs such as boceprevir and telaprevir [42]. Another issue which is still controversial is when to start treating the HCV recurrence [43]. The preemptive antiviral therapy after up to 6 months should be taken into consideration when rapidly progressive features emerge. The decision to treat post-LT HCV recurrence is often taken according to the histological characteristics (presence of fibrosis) at the 1-year liver biopsy, but at the same time, the individual patient's predictive factors of response should be carefully evaluated. The positive predictive characteristics associated with SVR are genotypes 2 or 3, mild fibrosis, young donor age, low baseline level of viremia, early viral clearance, and both donor and recipient CC polymorphism of IL28B [44–47]. The immunosuppressive regimen with cyclosporin has also been seen to be associated with SVR [48], but in triple regimens, especially those containing telaprevir, these data should be reviewed.

Undoubtedly, the oncoming era of HCV treatment has begun with the approval of several DAAs with different viral targets [49]. These drugs will likely very soon guarantee simplified treatment schedules and high tolerability and might avoid the use of interferon. Sofosbuvir is a potent all-oral-dosing nucleotide analogue inhibitor of HCV polymerase activity, with excellent virological response rates obtained in randomized controlled studies employing combination schedules with RBV, with or without PegIFN, in both naive and experienced HCV patients [50]. Currently, sofosbuvir is becoming more and more available worldwide but, besides the cost-related limitations, it should be noted that in LT settings, the experience is still limited. The preliminary data of a compassionate US program, utilizing sofosbuvir in LT recipients with a severe recurrence of HCV infection, were recently presented [51, 52], showing good clinical outcomes, a global clinical and MELD improvement; however, the relapse rate was not negligible, indicating that the treatment regimen should be maximally optimized in this seriously ill LT population, probably by combining sofosbuvir with another potent DAA. No drug-drug interactions with calcineurin inhibitors are expected during SOF administration [53, 54], but in a single center experience, awareness of significant tacrolimus/cyclosporine trough level reduction when sofosbuvir is administered in LT recipients has already emerged [55].

Indeed, the future perspectives of HCV-related viral hepatitis in pre-LT and post-LT settings will soon drastically change, thanks to the rich pipeline of new antiviral agents. However, some issues not present until now will affect real clinical practice and will require expert dedication in this complex setting. Among these, in addition to the time to treat and the duration of treatment, the most important are cost-effectiveness, choice of one DAA rather than another, drug-drug interactions, patients' eligibility for treatment, and viral resistance management. These features underline the importance of continuing to identify the predictive factors of good outcomes of antiviral treatment and of the global clinical outcomes in HCV-related viral hepatitis pre- and post-LT.

6.3 Liver Tumors

6.3.1 Hepatocellular Carcinoma

Fabio Piscaglia, Alessandro Cucchetti, Anna Pecorelli, and Luigi Bolondi

Liver cancer is the fifth most common malignancy among men and the ninth among women. In the last few years, it has risen from the third to the second cause of death from cancer, accounting for nearly 746,000 deaths in 2012, with an overall ratio of mortality to incidence of 0.95 [56]. The most common primary liver cancer is hepatocellular carcinoma (HCC), which occurs in the setting of liver cirrhosis in up to 90 % of cases [57].

The primary risk factor for HCC is still represented by chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection [58]. However, the advent of new antiviral drugs, the vaccination for HBV, and, on the other hand, the increasing incidence of obesity and metabolic syndrome are expected to reduce the burden of HCC on chronic viral liver disease and to increase the appearance of HCC on other causes of liver cirrhosis, such as nonalcoholic fatty liver disease (NAFLD) [58, 59]. Liver transplantation is the only curative treatment potentially able to eradicate both the tumor and the underlying liver disease. According to the European Liver Transplant Registry, 14 % of liver transplantations in Europe are performed in patients with HCC [60]. The first experiences of liver transplantation for HCC addressed patients with advanced HCC, producing poor outcomes as a consequence of extremely high posttransplant tumor recurrence rates. These results together with the shortage of available grafts led many transplant centers to select patients with defined criteria more accurately in order to guarantee better survival outcome.

In 1996, Mazzaferro and colleagues introduced the so-called Milan criteria. According to these criteria, initially documented by authors on pathological findings, patients with a single nodule <5 cm or up to three nodules <3 cm, with neither extrahepatic spread nor macrovascular invasion, could achieve a 5-year survival rate of 70 %, comparable to patients transplanted for nonmalignant liver disease [61], with tumor recurrence in less than 10 %. These criteria are still currently used in the Barcelona Clinic Liver Cancer (BCLC) HCC staging system, adopted in the majority of Western countries. This staging system stratifies patients according to liver function, tumor burden, and performance status, attempting to define, for each stage, the most effective treatment to adopt [62]. Patients within the Milan criteria correspond to the early HCC tumor stage.

Due to the excellent results achieved with use of the Milan criteria based on radiologic assessment, but also the clinical practice evidence of good outcome for some selected patients transplanted despite being beyond the Milan criteria, several transplant centers tried to expand the boundaries of liver transplantation for HCC in the last decade. In 2001, the University of California San Francisco (UCSF) group produced a prospective study to identify expanded criteria for liver transplantation for HCC. The outcome of patients inside UCSF criteria (one tumor $\leq$6.5 cm, or up to three nodules $\leq$4.5 cm, and total tumor diameter <8 cm) was comparable to that observed in other retrospective studies [63]. In 2009, a multicenter international

retrospective study coordinated by Mazzaferro showed comparable 5-year survival rates between patients within Milan criteria versus patients outside Milan criteria but fitting the so-called up-to-seven criteria (UtS) on pathology and without microvascular invasion. According to UtS, the sum of the number of tumors and the diameter of the largest nodule should not exceed seven, with no macrovascular invasion or extrahepatic spread [9] to achieve acceptable results in terms of recurrence rates and overall survival. Another new tool, the Metroticket calculator, has been created. This tool predicts the 5-year survival of patients on the basis of tumor burden according to the number and size of nodules and presence or absence of vascular invasion [64]. The major criticism regarding this tool is that its most important variable, namely, microvascular invasion, can be assessed only in the pathological specimen, thus once the liver transplant has already been performed.

An alternative strategy to simply expand the listing criteria based on tumor burden is to assess the tumor biology, and hence the risk of recurrence, on the basis of tumor response to hepatic resection or locoregional treatments, whose aim is to bring selected intermediate (BCLC-B) stage HCCs back to the early (BCLC-A) tumor stage. Good results have recently been achieved by using this downstaging procedure. Up to 2014, only two perspectives studies have been carried out, one of which was conducted at the University of Bologna; this latter experience obtained comparable survivals between transplanted patients successfully treated with downstaging and patients who always met the Milan criteria [65]. In this study, criteria for downstaging were identified as a single nodule ≤6 cm, or two nodules ≤5 cm, or less than six nodules ≤4 cm, with the sum of diameters ≤12 cm without macrovascular invasion or extrahepatic spread. However, clear limits for size and number of lesions as eligibility criteria for starting the downstaging procedure are still lacking, with the exception of extrahepatic spread and macrovascular invasion. After a successful downstage, a minimum period of 3 months is recommended before considering liver transplantation [66]. An alternative option to select out patients with expected worse survival and high recurrence rate is to use tumor grading. This approach excludes patients with poor tumor differentiation according to the Edmondson and Steiner criteria (G4) but requires aggressive and numerous tumor biopsies and has never been validated outside the proposing center [67].

The imbalance between demand and donor organ supply still remains the main issue in liver transplantation. Since 2001, patients on the waiting list are ranked on the basis of the Model for End-Stage Liver Disease (MELD) score. This score is based on serum bilirubin, creatinine, and international normalized ratio and indicates the three-month mortality rate in cirrhotic patients [68]. As the neoplastic risk is not considered in the MELD score, patients with HCC are given additional MELD exception points, which increase over time. According to the 2013 United Network for Organ Sharing (UNOS) allocation system, patients with a single HCC <2 cm do not receive additional points, while patients with a single HCC of 2–5 cm or with three nodules each <3 cm receive 22 points in addition to the original MELD score with a 10 % point increase for every 3 months on the waiting list [69]. Despite additional points, the dropout rate from the waiting list due to tumor progression is common, being approximately 10–20 % per year. A regular follow-up with an imaging

technique (CT or MRI) should therefore be performed every 3 months. An indirect measure of the tumor aggressiveness can be used to determine priority for transplantation. To date, there is growing evidence that cases with complete radiological response to pretransplant surgical and nonsurgical procedures will experience a lower dropout rate (tumor growth beyond transplantability criteria), and it is possible that in such cases, priority can be safely reduced, giving the remaining patients on the waiting list more chances of a transplant [70].

Locoregional treatments are commonly performed on patients awaiting liver transplantation as "bridge therapy" to prevent dropout. Currently, EASL-EORTC guidelines suggest bridge therapy if the waiting list time exceeds 6 months; however, there are no recommendations about the type of treatment [71]. The choice should be taken by a multidisciplinary team and tailored on the basis of tumor burden, liver function, and patient characteristics. In most countries, the expected waiting time exceeds 6 months for HCC, and all patients are aggressively treated for HCC, liver function permitting, in the prospect of transplantation, to prevent dropouts. Transcatheter arterial chemoembolization (TACE) is the most common bridge therapy, usually performed in patients with a single nodule >3 cm or multifocal HCCs. In the presence of decompensate liver function, TACE is contraindicated, and percutaneous ablative therapies, such as radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI), are preferred. However, RFA or PEI efficacy is limited to small HCCs (<2–3 cm). Liver resection should be the first-line therapy in the case of resectable HCCs in a setting of preserved liver function, normal portal pressure, and normal bilirubin. In the case of postoperative liver failure or HCC recurrence, liver transplantation can be reconsidered as "salvage transplantation," with outcomes comparable to primary liver transplantation [72]. However, clinically significant portal hypertension should not be considered an absolute contraindication but taken into account in the final decision, which has to consider liver function, usually in terms also of MELD score, and the extent of resection [73].

Another strategy to overcome deceased organ shortage and long waiting times is to use grafts from healthy living donors (LDLT). Although survival rates between LDLT and DDLT (deceased donor liver transplantation) are comparable, a high recurrence rate has been observed in LDLT. This could be due to the different waiting time, inherently longer in patients awaiting a DDLT, during which a tumor with a more aggressive behavior can be detected. Some authors suggest a 3-month period of observation to avoid transplantation of a more aggressive tumor [74, 75]. According to EASL guidelines, LDLT is an alternative option in patients with a waiting list time exceeding 6–7 months [68].

After liver transplantation, the main complication is the risk of HCC recurrence, which affects 8–20 % of the recipients. Recurrence is associated with poor outcome and a median survival less than 1 year after the diagnosis [74]. According to recent recommendations for liver transplantation for hepatocellular carcinoma, patients should be followed up with CT or MRI imaging and alpha-fetoprotein every 6–12 months after LT. HCC recurrence could be treated by surgery, locoregional therapy, and also systemic therapy, while retransplantation is not appropriate. As regards immunosuppression, mTOR inhibitors, in particular sirolimus, should be used due to their antineoplastic properties [76].

6.4 Cholestatic and Autoimmune Disease

Maria Cristina Morelli

6.4.1 Autoimmune Liver Diseases

The group of cholestatic and autoimmune disease usually includes autoimmune hepatitis (AH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC). Even if these diseases are infrequent, they represent a considerable proportion of patients in need of transplantation. The estimated prevalence of AH in the general population is 10–20/100,000, of PBC it is 40–60/100,000, and of PSC it is 10–30/100,000. The difficulty to reach a diagnosis and the need to exclude other causes of liver disease, such as hepatotropic infection but also systemic inflammation or drug-induced toxicity, are common in the context of autoimmune disease. Autoimmune liver disease may also overlap. The concomitant presence of PBC and AH features is a frequent finding, as is, although to a lesser extent, the overlap between PSC and AH. Another important issue is that overlap features may also change over time, and the patient may acquire other features many years after the first diagnosis; this is a very important aspect to consider as regards therapeutic implications. To date, there is no definitive treatments that can cure autoimmune disease; as a consequence, a considerable proportion of patients progressively develops liver failure requiring liver transplantation. In addition, all three autoimmune diseases can recur after liver transplantation and represent a greater risk of organ rejection.

6.4.2 Primary Biliary Cirrhosis (PBC)

Primary biliary cirrhosis is a chronic cholestatic liver disease characterized by immune-mediated destruction of small and medium intrahepatic bile ducts leading to cholestasis and cirrhosis. Primary biliary cirrhosis affects women in 90–95 % of cases and is often associated with other autoimmune diseases such as rheumatoid arthritis, scleroderma, and Sjogren's syndrome. A recent epidemiologic study reported that the lowest and highest incidences for PBC were both found in Newcastle-upon-Tyne in 1997 with 0.9 per 100,000 inhabitants per year in 1977 and 5.8 per 100,000 inhabitants per year in 1994, respectively. The highest prevalence for PBC is reported in a North American study published in 1995 with 40.2 per 100,000 age- and sex-matched inhabitants. Looking at the most recent epidemiological studies, the mean proportion of female patients was 92 % (76–100 %). Increasing trends of both incidence and prevalence of the disease are highlighted in studies from the United Kingdom, the United States, and Australia, but it is not clear whether the increase is true or just represents earlier recognition of the disease due to greater awareness and improved diagnostic workup [77].

Clinical presentation is often nonspecific, and symptoms include signs of cholestasis such as fatigue, skin pigmentation, jaundice, itching skin, and weight loss. Fatigue, the main symptom in patients with PBC, is usually characterized as excessive daytime somnolence and can impair quality of life. In a recent study, fatigue in woman with PBC was found to be independently associated with an increased risk of cardiac death [78]. Pruritus is reported by 20–70 % of patients and, in some cases, could be very disabling and, when intractable, may become an indication for liver transplantation. Diagnosis is based on clinical and biochemical features of cholestasis, highly specific antimitochondrial antibodies (AMAs) detection, and high IgM levels. A reduction in bone density is common in patients with PBC, with features of osteopenia and osteoporosis. Most patients with PBC have elevations of alkaline phosphatase, mild elevations of aminotransferases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) activity, and increased levels of immunoglobulin M; serum cholesterol levels are also often elevated. A rise in serum bilirubin and gamma globulins, with a fall in serum albumin and platelet count, is the early indicator of the development of cirrhosis and portal hypertension [79, 80]. Antimitochondrial antibodies in serum are highly sensitive and specific for PBC: their presence is detectable in nearly 95 % of PBC patients. Follow-up data from AMA-positive individuals without signs of liver disease suggest that autoantibodies arise several years before the onset of symptoms and have a high predictive value. Histology is characterized by a lymphocytic cholangitis and classically divided into four stages. Stage I is characterized by normal-sized triads with portal inflammation and subtle bile duct damage; granulomas are often detected. Stage II is characterized by the increase of periportal inflammation extending into the hepatic parenchyma and periportal fibrosis. Stage III is characterized by a distortion of the hepatic architecture with numerous fibrous septa. Stage IV is defined by a cirrhotic evolution. Liver biopsy is not always needed in patients with AMA positivity and typical biochemical profile since the additional information obtainable by histology is quite small. Histology is otherwise useful in patients who have high levels of antinuclear antibodies in order to assess the presence of an overlap syndrome that will require substantial modification of the therapeutic approach.

PBC is a chronic and a progressive disease, but the clinical features may vary greatly between patients. Patients can remain symptom-free for years with a low progressive disease or, conversely, can progress rapidly to a symptomatic and evolving disease. Presence of symptoms at diagnosis is an important determinant of disease progression and survival [81]. Many therapeutic agents have been proposed for primary biliary cirrhosis on the basis of different views of disease pathogenesis. The only currently established treatment for primary biliary cirrhosis is ursodeoxycholic acid (UDCA) 13–15 mg/kg a day, which can be subdivided into two or three doses [82]. A meta-analysis of randomized placebo-controlled studies of UDCA concluded that about 20 % of patients treated with UDCA will have no histological progression over 4 years, and some will have no progression over a decade or longer [83]. This agent has the potential to reduce liver damage and, consequently, to prevent the development of portal hypertension and the need for transplantation. Survival free from liver transplantation seems to be improved in patients treated

with UDCA compared with patients originally assigned to placebo, in particular in medium- and high-risk groups of patients (serum bilirubin level, 1.4–3.5 or >3.5 mg/dL and histological stage IV subgroup) [84].

Liver transplantation is a definite therapeutic option in patients with PBC not only when patients decompensate as a cause of cirrhosis development but also in other condition such as treatment-resistant itching. Liver transplantation has been proved to improve fatigue and pruritus; the bone disease can worsen initially but improves in the subsequent periods. Surprisingly, the increase trend of incidence and prevalence of PBC is in contrast with the decrease of liver transplantation burden for this indication, despite an increase in total liver transplants [85]. The explanation for this trend is not clear but may be associated with a more efficacious therapy or a changing disease phenotype. Primary biliary cirrhosis after transplant has been described in 15–30 % of recipients, but only a low percentage evolved into graft failure. The Birmingham study reported a 2–3 % rate of graft loss for PBC recurrence over 15 years. Autoantibodies AMA may persist after liver transplantation but do not seem to be associated with recurrence of the disease.

6.4.3 Primary Sclerosing Cholangitis (PSC)

Primary sclerosing cholangitis is characterized by progressive inflammation of the intra- and extrahepatic bile ducts with progressive stenosis and obliteration of ducts leading to the development of secondary biliary cirrhosis, portal hypertension, and, finally, toward liver failure. It is characterized by a strong association (75–80 % of cases) with inflammatory bowel disease (IDB), mainly ulcerative colitis. Immunological mechanisms are involved in the pathogenesis of this disease, and consistent data show that PSC is an immune-mediated inflammatory disease rather than an autoimmune disease by itself. In favor of this hypothesis is the male prevalence, the failure to identify specific autoantigens, and lack of response to immunosuppressive therapy. It is currently accepted that, in an immunologically predisposed patient, antigens derived from bacteria may migrate into the portal circulation due to increased permeability of the colonic wall. Activation of Kupffer cells leads to cytokine and chemokine release with recall of inflammatory infiltrate (granulocytes, lymphocytes, macrophages, and fibroblasts) into the portal and peri-biliary space, resulting in fibrosis and, finally, in secondary biliary cirrhosis.

Primary sclerosing cholangitis is a relatively rare disease. Epidemiological studies published so far are few and are mainly derived from tertiary hospitals resulting from IBD prevalence rates. The first epidemiological study in the general population was conducted in Norway and published in 1998 [86]. This study reported an incidence of 1.3/100,000/year and a prevalence of 8.7/100,000. In 71 % of cases, there was an association with IBD; the male/female ratio was 3.3/1, and the mean age at the onset of the disease was 40 years [10]. At diagnosis, the majority of PSC patients are asymptomatic, and studies published in recent years reveal an increasing proportion of cases diagnosed in the asymptomatic phase. Most asymptomatic patients develop symptoms after 5–7 years. Symptoms are frequently nonspecific including fatigue,

jaundice, pruritus, and weight loss; fat-soluble vitamin deficiency, steatorrhea, and osteoporosis are rarer. Bacterial cholangitis and gallstones are specific symptoms related to development of biliary stenosis. Finally, patients can develop liver cirrhosis with hepatic failure; in addition, PSC has to be considered a preneoplastic condition with a high risk of cholangiocarcinoma development (100 times higher than the general population) and a higher risk of colorectal cancer in patients with coexistent ulcerative colitis than in patients with isolated ulcerative colitis. Thus, these aspects have to be considered from a transplantation perspective. The cholangiographic features of alternate extra- and intrahepatic bile duct stenosis and dilatation are the gold standard for the diagnosis of PSC. Because of its noninvasive nature, magnetic resonance imaging (MRI) may have advantages over invasive cholangiography when diagnosis is the major goal of the procedure, showing in recent studies 88 % sensitivity and 99 % specificity. In the presence of specific radiological features, liver biopsy is not considered essential because of the low diagnostic accuracy; furthermore, the typical histological lesions such as periductal "onion skin" fibrosis are detectable only in 13 % of cases. Histological examination is useful in suspected overlap syndrome and in the diagnosis of PSC involving only small ducts.

At present, there is no effective medical therapy modifying the natural history of PSC. The drug most studied and proposed in trials is ursodeoxycholic acid that, despite the proven anti-cholestatic effect, has not so far been proven effective in improving survival. UDCA has been proposed to decrease the risk of colorectal neoplasia in patients with PSC and ulcerative colitis based on results from retrospective studies. However, these studies had inconsistent results, so UDCA has not been recommended as a chemopreventive agent for patients with PSC-IBD [87, 88]. Liver transplantation is currently the only effective treatment option in PSC. PSC is the first indication for transplantation in Scandinavian countries and the fifth in the United States and constitutes less than 2 % of the indications for transplantation in Italy. The survival of the graft and the recipient is over 90 % at 1 year and 75 % at 15 years. The timing of transplantation is particularly difficult to define in PSC due to the unpredictability of certain events, such as the development of cholangiocarcinoma that is currently a contraindication to transplantation because of the high mortality caused by the high rate of recurrence. The criteria currently accepted for inclusion on the waiting list for liver transplantation are (1) jaundice or stenosis that cannot be treated endoscopically, (2) recurrent cholangitis, (3) decompensated cirrhosis (MELD score >13), or (4) a predicted 1-year survival <90 % according to the Mayo Clinic score [89].

The recurrence of PSC after liver transplantation has a wide variability in different series, but it affects approximately 20 % of patients, with a rate of retransplantation of about 5 %. The factors most frequently associated with the development of relapse are preservation damage, steroid-resistant rejection episodes, and previous treatment with OKT3.

Over the years, some prognostic scores have been proposed with the aim of predicting survival, defining the effectiveness of therapy, and establishing the timing of transplantation. Among the prognostic models, the score from the Mayo Clinic is the most commonly accepted as valid on a very large number of patients, and it is the only one that does not need a histological score. This model divides patients into low

(score <0), medium (score 0–2), and high risk (score >2), to predict the survival of 1 year and, consequently, to provide indications for the timing of liver transplantation. The formula of PSC-Mayo Risk score is the following: score = (0.0295 * (age in years)) + (0.5373 * LN(total bilirubin in mg/dL)) – (0.8389 * (serum albumin in g/dL)) + (0.5380 * LN(AST in IU/L) + (1.2426 * (points for variceal bleeding)).

6.4.4 Autoimmune Hepatitis and Cirrhosis

Autoimmune hepatitis (AH) is a characteristic autoimmune condition characterized by a strong female prevalence, presence of autoantibodies, frequently concomitant autoimmune diseases such as autoimmune thyroiditis or rheumatoid arthritis, and good response to corticosteroids. Two types of AIH are described: type 1 (AH-1), characterized by antinuclear antibodies (ANA) and/or anti-smooth muscle positivity, and type 2 (AH-2), characterized by anti-liver kidney microsomal type 1 antibody (anti-LKM-1) or for anti-liver cytosol type 1 antibody (anti-LC-1). Autoimmune hepatitis can occur in all geographical areas and is an infrequent disease, with a low prevalence (1:10,000 both in Western and Eastern countries). The clinical manifestations of autoimmune hepatitis can range from a subclinical disease, diagnosed occasionally with detection of high levels of liver enzymes, to an acute or fulminant hepatitis requiring urgent transplantation or to a progressive course toward cirrhosis. Diagnosis is based on four major criteria: elevated IgG levels (or total gamma globulins), characteristic autoantibodies, histological features of hepatitis, and absence of viral etiology. Response to immunosuppression is characteristic and supports the diagnosis. Randomized trials definitely showed the benefit of steroid treatment in patients with autoimmune hepatitis, documenting that 5-year survival rises to 25 % in untreated patients versus 80 % in those treated with corticosteroids [90, 91]. Liver transplantation can represent a treatment option also in acute or chronic patients who fail to respond to immunosuppressive therapy and in patients who develop end-stage liver disease. Liver transplantation is associated with excellent 5-year and 10-year survival rates. Recurrent autoimmune hepatitis following liver transplantation has been reported in approximately 15–30 % of adults and 33 % of children but rarely progresses to graft failure.

6.4.5 Cholestasis in the Newborn and Infant

Neonatal cholestasis occurs in approximately 1 in 2,500 term infants. A large number of causes for neonatal cholestasis have been identified, and they can be classified as follows: extrahepatic (biliary atresia, choledocal cyst, Alagille syndrome, biliary sludge, cystic fibrosis PSX, and congenital fibrosis/Caroli's disease) and intrahepatic (progressive familial intrahepatic cholestasis, giant cells hepatitis, viral hepatitis (HHV-6, HPV, CMV), alpha 1-antritrypsine deficiency, galactosemia, and tyrosinemia).

The most common causes of cholestatic jaundice in the first months of life are biliary atresia and neonatal hepatitis, which account for most cases. Alpha 1-antitrypsin deficiency causes another 5–15 % of cases. Remaining cases are caused by a variety of other disorders, including common duct gallstones or choledochal cyst; metabolic disorders such as tyrosinemia, galactosemia, and inborn errors of bile acid metabolism; Alagille syndrome; infection; and other rare disorders. Biliary atresia is characterized by obliteration or discontinuity of the extrahepatic biliary system, resulting in obstruction to the bile outflow of bile. This is a surgically treatable form of cholestasis during the neonatal period that, if not surgically corrected, progresses toward biliary cirrhosis. Patients with biliary atresia can be divided into two distinct groups: those with the isolated form of biliary atresia (65–90 % of cases) and those associated with situs inversus, a congenital condition in which the major visceral organs are reversed or mirrored from normal positions. The pathogenesis of this disease is not fully known. Early studies have suggested a congenital malformation of the bile duct system. Before liver transplant became the only therapeutic option for children with end-stage liver disease, the survival of children treated with portoenterostomy was 47–60 % at 5 years and 25–35 % at 10 years [92]. Neonatal giant cell hepatitis (NGCH) is an acute cholestatic disease of unknown etiology. Clinical features are usually hepatomegaly, jaundice, dark urine, acholic stools, and liver insufficiency up to fulminant hepatitis. Liver histology shows giant hepatocytes that appear as a common liver response to many types of damage in the neonatal period. Infectious agents causing giant cell transformation include hepatitis with hemolytic anemia, paramyxovirus (syncytial giant cell hepatitis), hepatitis with rubeola infection, and hepatitis with HIV infection; cytomegalovirus (CMV), human papillomavirus (HPV), and herpesvirus 6 (HHV6) have recently been linked to NGCH [93, 94].

6.5 Other Liver Tumors

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6.5.1 Malignant Tumors Other than Hepatocellular Carcinoma

At the beginning of the liver transplantation (LT) experience, liver malignancies represented an optimal indication to transplantation since liver replacement represents the most radical operation; however, the use of immunosuppression therapy increases tumor recurrence at an unacceptable rate [95]. Furthermore, considering that the pool of deceased donors is not sufficient to meet the need for organs, it is important to apply a resectional strategy whenever possible, leaving LT as an option in cases of unresectable liver tumors and when acceptable long-term results can be expected [65, 96]. Except for hepatocellular carcinoma (HCC) which remains one of the main indications for LT, transplantation has been applied as a treatment strategy for other malignant hepatic tumors.

6.5.1.1 Cholangiocarcinoma

In the 1990s, the initial clinical experience of LT for unresectable cholangiocarcinoma yielded poor long-term results, with 5-year survival ranging between 18 and 38 % [97–99]. After the promising experience at the University of Pittsburgh with a 5-year survival of more than 50 % [100, 101], the Mayo Clinic developed a protocol of strict recipient selection and neoadjuvant chemoirradiation, which produced unexpected positive outcomes [102]. The neoadjuvant treatment protocol consists of extended beam radiation (4,500 cGy/day for 15 days) and protracted intravenous infusion of 5-FU (225 mg/m^2/day). Biliary brachytherapy will then deliver 2,000 cGy, and finally, oral capecitabine (1,000 mg/m^2/day 2 out of every 3 weeks) is administered until LT. A staging laparotomy is performed before LT in order to rule out the presence of intra- or extrahepatic metastases and lymph node metastases. Both a meta-analysis on 605 transplanted patients for CCC in 14 American and European centers and a recent review summarizing the results in patients treated before and after the "Mayo Protocol" have confirmed the dismal results of 5-year survival around 17–35 % in previous series and the encouraging results of 5-year survival up to 75 % in the most recent cases treated by the neoadjuvant scheme [103, 104]. These data suggest that cholangiocarcinoma may be no longer considered an absolute contraindication for OLT. It has several advantages over liver resection because it allows a complete negative resection margin when the anatomical location would not allow a radical resection and particularly in patients with chronic underlying liver disease (like sclerosing cholangitis) who may not tolerate partial hepatectomy.

Although encouraging results have been obtained, a few concerns need to be discussed before considering cholangiocarcinoma as a routine indication for OLT. The first issue is the high dropout rate associated with some tumor characteristics [105], such as Ca 19–9 over 500 U/mL, mass diameter >3 cm, bioptic evidence of malignancy, and MELD score >20. The second issue is that it is not clear whether the absence of tumors in the explanted livers after chemoradiation in half of the cases was due to the efficacy of the neoadjuvant treatment or an initial false-positive diagnosis. Finally, recent series from the Universities of Seoul and Nagoya showed that biliary drainage associated with portal vein embolization could allow extended hepatectomy with acceptable mortality and, in cases with R0 resection and negative lymph nodes, a 5-year survival up to 50 % [106, 107]. Considering that the main prognostic factors after liver resection are the same as those that would be contraindications for LT, it can be concluded that hepatic resection is still the main therapeutic strategy and that LT, since the Mayo Protocol, can be considered an option in selected cases of cholangiocarcinoma, when liver function is impaired due to underlying liver disease (primary sclerosing cholangitis [PSC]).

Both intra- and extrahepatic CCA could represent indications for LT when resective surgery is not an option because of underlying liver disease or anatomically unresectable lesions. Liver transplantation may offer better results than palliative therapy if the radial diameter of the intrahepatic mass is under 3 cm, a staging laparotomy is performed, and no extrahepatic or lymph node metastases are detected [105].

6.5.1.2 Neuroendocrine Liver Metastases

LT has been mainly proposed for unresectable neuroendocrine liver tumors (NET) [108]. Currently, in the presence of multiple new alternative medical treatments and due to the relative long-term prognosis for this disease, the real survival benefit of LT over other techniques is unknown, and comparative studies are needed. A recent multicenter study from 35 transplant centers enrolling 213 patients showed a 5-year survival over 50 % [109]. From data reported in the literature [109–112], LT may be performed when (1) the disease is limited to the liver and the primary tumor has been removed (the primary tumor should be removed before OLT, since an unknown primary tumor and exeresis at the time of OLT are negative prognostic factors); (2) well-differentiated tumors, measured with a Ki67 <10 %; (3) no major extrahepatic resections are required; and (4) the patient has been followed up from the time of diagnosis for 1–2 years to evaluate biological behavior.

6.5.1.3 Colorectal Metastases

These have been considered an absolute contraindication to OLT due to dismal long-term results; however, a recent Norwegian series of 21 transplanted patients reported a 5-year survival of 60 % even with an almost universal recurrence after OLT [113]. The use of mTOR inhibitors and of strict selection criteria may encourage new controlled studies to evaluate the usefulness of OLT for this set of patients.

6.5.1.4 Hepatoblastoma

This is the most frequent hepatic primary tumor in children; it is often diagnosed at an advanced stage (tumor spread involving both lobes) when surgical resection is not possible; in these cases, LT is the only therapeutic option. A recent review coming from data in the United States showed a 5-year survival exceeding 75 % and a recurrence rate of 16 % [114] suggesting that improved survival could be obtained if a precise preoperative workup and an adequate chemotherapeutic regimen can be applied.

6.5.1.5 Hepatic Hemangioendothelioma

This is a rare tumor derived from endothelial cells which often presents as multifocal disease, with an intermediate clinical course between benign hemangioma and malignant angiosarcoma [115]. Tumor resection is the gold standard; poor results have been reported with chemotherapy and radiotherapy. However, the multifocality of the disease makes a curative resection rarely possible, and LT becomes an effective and frequent option with a 5-year survival ranging from 53 % up to 80 % [115, 116]. Lymph node invasion and minimal extrahepatic disease are not absolute contraindications for transplantation. Only the presence of macroscopic vascular invasion significantly affects long-term outcome [115]. The main challenge remains the differential diagnosis with hemangiosarcoma which has, on the contrary, a very poor outcome: a recent review from the ELTR reported an overall survival of 7 months after OLT for hemangiosarcoma [117]. The immunostaining analysis and a 6-month waiting list observation period may help in avoiding unuseful transplantation.

6.5.2 Benign Tumors

Benign liver tumors are a quite common disease reported in almost 20 % of the US population [118] and are the indication for hepatic resections in about 6 % of patients [119]. Liver transplantation has been reported as the treatment of several benign hepatic tumors which are listed in Table 6.1. Reasons for LT were uncertain diagnosis or preneoplastic lesions with a high risk of malignant transformation, association with metabolic diseases or Kasabach-Merritt syndrome, and abdominal encumbrance. However, there is a lack of data regarding the optimal indications for LT. Due to the high morbidity, the still significant mortality and the shortage of donor grafts, indications for LT remain far from being standardized. In such instances, conservative management and surgical resection remain the most adopted clinical strategies [115]. UNOS and ELTR data report the indication for benign liver tumors in about 1 % of all LT with a 5-year survival close to 75 % [115, 120, 121]. The majority of cases were performed due to polycystic disease (about 70 % of all cases of benign liver tumors); other less common indications were hepatic adenoma and adenomatosis, cavernous hemangioma, nodular regenerative hyperplasia, and other rare tumors.

6.5.2.1 Polycystic Liver Disease

Autosomal dominant polycystic disease is genetically heterogeneous, with mutations in two distinct genes (PKD1 and PKD2) predisposing to combined polycystic liver and kidney disease and mutation in a third gene, protein kinase C substrate 80K-H (PRKCSH), accounting for a rare isolated polycystic liver disease without renal involvement [115, 122]. The severity of polycystic liver disease often correlates with the severity of renal cystic disease and the degree of renal dysfunction [115]. Most patients are asymptomatic; however, in a few patients, massive and large cysts may cause abdominal pain, discomfort, and shortness of breath [122]. Radiologic cyst aspiration or sclerosis has been applied with various degrees of success and cyst recurrence; complete cyst fenestration by laparotomy or surgical resection has led to a complete, sustained resolution of symptoms but is associated with prolonged hospitalization and significant morbidity. For this reason, cyst fenestration by laparoscopic approach is the preferred option with less morbidity and hospitalization even though a significant recurrence of symptoms has been reported [122]. Liver transplantation offers the best chance of definitive treatment in patients where the presence of massive and large cysts can cause life-threatening symptoms such as malnutrition, weight loss, asthenia, and reduction of oral intake. Symptomatic polycystic liver disease with end-stage renal cyst disease is considered for combined liver-kidney transplantation [123].

Except for a high postoperative risk, long-term results have been reported as satisfactory [124, 125]. The increased risk of sepsis might have been due to bacterial reservoirs in cysts and/or prolonged poor nutritional status, amplified by the immunosuppressive agents [115]. A recent German study analyzed the quality of life after LT and showed that most of these patients (91 %) can report an improvement in social status and better quality of life compared to before LT; 78 % of patients said

they would opt for transplantation again [126]. The risk of developing severe cachexia and malnutrition, the excellent long-term results with dramatic improvements in quality of life, and the unreliable representation by the MELD score due to the absence of signs of liver failure suggest the need for earlier transplantation, avoiding putting the patient on the waiting list too late.

6.5.2.2 Liver Cell Adenoma and Liver Cell Adenomatosis

Liver cell adenoma is increasingly seen due to the widespread use of estrogen-based oral contraceptives (incidence of 3 per 1,000,000 per year) [127]. Symptomatic patients usually present with right upper quadrant pain and normal liver function tests. Spontaneous bleeding is a well-recognized complication which is often the cause of pain. Another serious complication is the risk of malignant transformation in about 5 % of patients [128, 129]. Liver transplantation has rarely been reported in the treatment of solitary giant adenoma [120, 121]. With the improvements of surgical techniques and perioperative management, surgical resection is considered the treatment of choice for solitary liver cell adenomas larger than 5 cm or complicated by hemorrhage or malignant transformation, and LT should be abandoned.

Multiple adenomas occur in 10–24 % of all patients with liver cell adenomas, forming a new clinical entity known as "liver cell adenomatosis" which was first described in 1985 by Flejou [130]. The typical clinical findings of liver adenomatosis are the presence of multiple adenomas (arbitrarily more than three or ten), no association with oral contraceptives, no history of glycogen storage disease, predominant in women, and with unknown etiology [131]. Intra-tumoral or intraperitoneal hemorrhage can be present in 46–63 % of patients and is much more frequent compared to patients with solitary liver adenoma; malignant transformation is less frequent. The risk of complication seems to be related more to the diameter of the largest nodule than to the number of nodules. The management of liver adenomatosis remains problematic. OLT has been reported in 6 % of published series of liver adenomatosis and in more than 5 % of liver transplantations performed for benign liver tumors in the United States and Europe [120, 121]. All technical procedures should be used, including portal vein embolization, to allow even extensive resections and remove most nodules, especially the larger ones. After the surgical approach, around 25 % patients need a second operation, and 43 % of the remaining adenomas continue to grow [132]. In rare progressive symptomatic forms with massive liver involvement and/or serious repeated complications, liver transplantation might be considered as the last therapeutic option [115].

6.5.2.3 Liver Hemangioma

Cavernous hepatic hemangioma is the most frequent benign liver tumor with a prevalence in autopsy and imaging studies of up to 7 % [133]. The majority of hepatic hemangiomas should be managed conservatively. In a few cases of giant hemangioma refractory to analgesics and with worsening abdominal pain or symptoms due to mechanical compression of adjacent organs, surgical resection is indicated [115]. Liver transplantation has been reported in very rare cases of huge hemangiomas [134]. According to a recent review, only 12 cases have been reported in the English

literature, and most of them were associated with the presence of Kasabach-Merritt syndrome [134]. Liver transplantation seems to be a very rare indication and is required only in exceptional cases.

6.5.2.4 Caroli's Disease

This is a rare congenital disease characterized by gross segmental dilatation of the intrahepatic bile ducts causing a macroscopic appearance of intrahepatic multiple cysts; it is included in type IVa and V of Todani's classification for choledochal cysts and combined with polycystic renal disease in a few cases [135]. It can be associated with hepatic fibrosis which is a different entity, named Caroli's syndrome [136]. Early postoperative outcome has been affected by a high incidence of septic and vascular complications; however, the long-term outcome in patients surviving more than 1 year after OLT was excellent [136, 137]. From the data available in the literature, LT should be advocated earlier during the natural history of the "diffuse type" of Caroli's disease with recurrent biliary infections or when associated with hepatic fibrosis.

6.5.2.5 Nodular Regenerative Hyperplasia

NRH is an uncommon disease characterized by the presence of multiple, small non-fibrotic nodules (less than 1 cm) probably due to vascular abnormalities which are the main cause of intrahepatic noncirrhotic portal hypertension [138]. A few cases of OLT have been reported in the literature [138]. In most patients, successful long-term outcome was achieved. Recurrent nodular regenerative hyperplasia has been reported in the graft, but only rarely, retransplantation was needed.

Other rare indications for liver transplantation for benign hepatic tumors massively involving the liver are mesenchymal hamartoma, alveolar echinococcosis, inflammatory pseudotumors, and hepatic lymphangiomatosis [139, 140].

References

1. US Scientific Registry (UNOS). Richmond (VA): United Network for Organ Sharing. 2014. http://www.unos.org/.
2. Lee WM. Acute liver failure. NEJM. 1993;329:1862–72.
3. Bailey B, Amre DK, Gaudreault P. Fulminant hepatic failure secondary to acetaminophen poisoning: a systematic review and meta-analysis of prognostic criteria determining the need for liver transplantation. Crit Care Med. 2003;31:299–305.
4. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology. 1989;97:439–45.
5. Macquillan GC, Seyam MS, Nightingale P, Neuberger JM, Murphy N. Blood lactate but not serum phosphate levels can predict patient outcome in fulminant hepatic failure. Liver Transpl. 2005;11:1073–9.
6. Nazer H, Ede RJ, Mowat AP, Williams R. Wilson's disease: clinical presentation and use of prognostic index. Gut. 1986;27:1377–81.
7. Dhawan A, Taylor RM, Cheeseman P, De Silva P, Katsiyiannakis L, Mieli-Vergani G. Wilson's disease in children: 37-year experience and revised King's score for liver transplantation. Liver Transpl. 2005;11:441–8.

8. Rao W, Wu X, Xiu D. Lamivudine or lamivudine combined with hepatitis B immunoglobulin in prophylaxis of hepatitis B recurrence after liver transplantation: a meta-analysis. Transpl Int. 2009;22:387–94.
9. Katz LH, Paul M, Guy DG, Tur-Kaspa R. Prevention of recurrent hepatitis B virus infection after liver transplantation: hepatitis B immunoglobulin, antiviral drugs, or both? Systematic review and meta-analysis. Transpl Infect Dis. 2010;12:292–308.
10. Lucey MR, Graham DM, Martin P, et al. Recurrence of hepatitis B and delta hepatitis after orthotopic liver transplantation. Gut. 1992;33:1390–6.
11. O'Grady JG, Smith HM, Davies SE, et al. Hepatitis B virus reinfection after orthotopic liver transplantation. Serological and clinical implications. J Hepatol. 1992;14:104–11.
12. Schiff E, Lai CL, Hadziyannis S, et al. Adefovir dipivoxil for waitlisted and post-liver transplantation patients with lamivudine-resistant hepatitis B: final long-term results. Liver Transpl. 2007;13:349–60.
13. Liaw YF, Raptopoulou-Gigi M, Cheinquer H, et al. Efficacy and safety of entecavir versus adefovir in chronic hepatitis B patients with hepatic decompensation: a randomized, open-label study. Hepatology. 2011;54:91–100.
14. Liaw YF, Sheen IS, Lee CM, et al. Tenofovir disoproxil fumarate (TDF), emtricitabine/TDF, and entecavir in patients with decompensated chronic hepatitis B liver disease. Hepatology. 2011;53:62–72.
15. Lange CM, Bojunga J, Hofmann WP, et al. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. Hepatology. 2009;50:2001–6.
16. Samuel D, Muller R, Alexander G, et al. Liver transplantation in European patients with the hepatitis B surface antigen. N Engl J Med. 1993;329:1842–7.
17. Cholongitas E, Goulis J, Akriviadis E, et al. Hepatitis B immunoglobulin and/or nucleos(t)ide analogues for prophylaxis against hepatitis b virus recurrence after liver transplantation: a systematic review. Liver Transpl. 2011;17:1176–90.
18. Loomba R, Rowley AK, Wesley R, et al. Hepatitis B immunoglobulin and Lamivudine improve hepatitis B-related outcomes after liver transplantation: meta-analysis. Clin Gastroenterol Hepatol. 2008;6:696–700.
19. Lenci I, Tisone G, Di Paolo D, et al. Safety of complete and sustained prophylaxis withdrawal in patients liver-transplanted for HBV-related cirrhosis at low risk of HBV recurrence. J Hepatol. 2011;55:587–93.
20. Fung J, Cheung C, Chan SC, et al. Entecavir monotherapy is effective in suppressing hepatitis B virus after liver transplantation. Gastroenterology. 2011;141:1212–9.
21. Angelico M, Di Paolo D, Trinito MO, et al. Failure of a reinforced triple course of hepatitis B vaccination in patients transplanted for HBV-related cirrhosis. Hepatology. 2002;35:176–81.
22. EASL. Clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol. 2012;57:167–85.
23. Cholongitas E, Papatheodoridis GV, Burroughs AK. Liver grafts from anti-hepatitis B core positive donors: a systematic review. J Hepatol. 2010;52:272–9.
24. Adam R, McMaster P, O'Grady JG, European Liver Transplant Association, et al. Evolution of liver transplantation in Europe: report of the European Liver Transplant Registry. Liver Transpl. 2003;9(12):1231–43.
25. Garcia-Retortillo M, Forns X, Feliu A, Moitinho E, Costa J, Navasa M, Rimola A, Rodes J. Hepatitis C virus kinetics during and immediately after liver transplantation. Hepatology. 2002;35(3):680–7.
26. Terrault NA, Berenguer M. Treating hepatitis C infection in liver transplant recipients. Liver Transpl. 2006;12:1192–204.
27. Berenguer M, Prieto M, Rayón JM, et al. Natural history of clinically compensated hepatitis C virus-related graft cirrhosis after liver transplantation. Hepatology. 2000;32(4 Pt 1):852–8.

28. Carrión JA, Navasa M, Garcia-Retortillo M, et al. Efficacy of antiviral therapy on hepatitis C recurrence after liver transplantation: a randomized controlled study. Gastroenterology. 2007;132:1746–56.
29. Veldt BJ, Poterucha JJ, Watt KD, et al. Impact of pegylated interferon and ribavirin treatment on graft survival in liver transplant patients with recurrent hepatitis C infection. Am J Transplant. 2008;8:2426–33.
30. Roche B, Sebagh M, Canfora ML, et al. Hepatitis C virus therapy in liver transplant recipients: response predictors, effect on fibrosis progression, and importance of the initial stage of fibrosis. Liver Transpl. 2008;14:1766–77.
31. Berenguer M, Palau A, Aguilera V, et al. Clinical benefits of antiviral therapy in patients with recurrent hepatitis C following liver transplantation. Am J Transplant. 2008;8:679–87.
32. Berenguer M. Systematic review of the treatment of established recurrent hepatitis C with pegylated interferon in combination with ribavirin. J Hepatol. 2008;49:274–87.
33. Jacobson IM, McHutchison JG, Dusheiko G, ADVANCE Study Team, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011;364:2405–16.
34. Zeuzem S, Andreone P, Pol S, REALIZE Study Team, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011;364(25):2417–28.
35. Werner CR, Egetemeyr DP, Lauer U, et al. Telaprevir-based triple therapy in liver transplant patients with hepatitis C virus: a 12-week pilot study providing safety and efficacy data. Liver Transpl. 2012;18:1464–70.
36. Burton Jr JR, O'Leary JG, Verna EC, et al. A US multicenter study of hepatitis C treatment of liver transplant recipients with protease-inhibitor triple therapy. J Hepatol. 2014. doi:10.1016/j.jhep.2014.04.037. pii: S0168-8278(14)00300-6.
37. Coilly A, Roche B, Duclos-Vallée JC, Samuel D. Management of HCV transplant patients with triple therapy. Liver Int. 2014;34 Suppl 1:46–52. doi:10.1111/liv.12406.
38. Coilly A, Roche B, Dumortier J, et al. Safety and efficacy of protease inhibitors to treat hepatitis C after liver transplantation: a multicenter experience. J Hepatol. 2014;60(1):78–86. doi:10.1016/j.jhep.2013.08.018. Epub 2013 Aug 29.
39. Coilly A, Furlan V, Roche B, et al. Practical management of boceprevir and immunosuppressive therapy in liver transplant recipients with hepatitis C virus recurrence. Antimicrob Agents Chemother. 2012;56(11):5728–34. doi:10.1128/AAC.01151-12. Epub 2012 Aug 20.
40. Ikegami T, Yoshizumi T, Shirabe K, Maehara Y. Frequent plasma cell hepatitis during telaprevir-based triple therapy for hepatitis C after liver transplantation. J Hepatol. 2014;60(4):894–6.
41. Coilly A, Sebagh M, Duclos-Vallée JC. Reply to: "frequent plasma cell hepatitis during telaprevir-based triple therapy for hepatitis C after liver transplantation". J Hepatol. 2014;60(4):896–7. doi:10.1016/j.jhep.2013.11.032.
42. Saxena V, Monto A, Terrault N. Commentary: treatment of hepatitis C-related cirrhosis in the era of direct-acting anti-virals – authors' reply. Aliment Pharmacol Ther. 2014;39(12):1428. doi:10.1111/apt.12775.
43. Roche B, Samuel D. Is early antiviral therapy for recurrent hepatitis C after liver transplantation superior to later treatment? The answer is no. Liver Transpl. 2011;17:488–91.
44. Charlton MR, Thompson A, Veldt BJ, et al. Interleukin-28B polymorphisms are associated with histological recurrence and treatment response following liver transplantation in patients with hepatitis C virus infection. Hepatology. 2011;53:317–24.
45. Lange CM, Moradpour D, Doehring A, et al. Impact of donor and recipient IL28B rs12979860 genotypes on hepatitis C virus liver graft reinfection. J Hepatol. 2011;55:322–7.
46. Coto-Llerena M, Perez-Del-Pulgar S, Crespo G, et al. Donor and recipient IL28B polymorphisms in HCV-infected patients undergoing antiviral therapy before and after liver transplantation. Am J Transplant. 2011;11:1051–7.
47. Fukuhara T, Taketomi A, Motomura T, et al. Variants in IL28B in liver recipients and donors correlate with response to peg-interferon and ribavirin therapy for recurrent hepatitis C. Gastroenterology. 2010;139:1577–85.

48. ReViS-TC Study Group. Cyclosporine A-based immunosuppression reduces relapse rate after antiviral therapy in transplanted patients with hepatitis C virus infection: a large multicenter cohort study. Transplantation. 2011;92:334–40.
49. Casey LC, Lee WM. Hepatitis C virus therapy update 2013. Curr Opin Gastroenterol. 2013;29(3):243–9.
50. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, Hindes RG, Berrey MM. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. NEJM. 2013;368:34–44.
51. Forns X, Fontana RJ, Moonka D, et al. Initial evaluation of the sofosbuvir compassionate use program for patients with severe recurrent HCV following liver transplantation. 64th annual meeting of the American Association for the Study of Liver Diseases. 2013.
52. Samuel D, Charlton M, Gane E, et al. Sofosbuvir and ribavirin for the treatment of recurrent hepatitis c infection after liver transplantation: results of a prospective, multicenter study. Gastroenterol. 2015;148(1):108–17. http://dx.doi.org/10.1016/S0168-8278(14)61392-1.
53. Mathias A, Cornpropst M, Clemons D, Denning J, Symonds WT. No clinically significant pharmacokinetic drug-drug interactions between sofosbuvir (GS-7977) and the immunosuppressants, cyclosporine A or tacrolimus in healthy volunteers (abstract 1869). 63rd annual meeting of the American Association for the Study of Liver Diseases. 2012.
54. Koff RS. Review article: the efficacy and safety of sofosbuvir, a novel, oral nucleotide NS5B polymerase inhibitor, in the treatment of chronic hepatitis C virus infection. Aliment Pharmacol Ther. 2014;39:478–87.
55. Vukotic R, Morelli MC, Pinna AD, et al. Letter: calcineurin inhibitor level reduction during treatment with sofosbuvir in liver transplanted patients. Aliment Pharmacol Ther. 2014. doi:10.1111/apt.12853.
56. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11, Lyon, France: International Agency for Research on Cancer; 2013 [Internet]. Available from: http://globocan.iarc.fr. Cited 2014 Mar 22.
57. Schütte K, Bornschein J, Malfertheiner P. Hepatocellular carcinoma–epidemiological trends and risk factors. Digestive diseases [Internet] 2009. Available from: http://www.karger.com/Article/Fulltext/218339.
58. Bosch FX, Ribes J, Cléries R, Díaz M. Epidemiology of hepatocellular carcinoma. Clin Liver Dis. 2005;9:191–211.
59. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology. 2007;132:2557–76.
60. European Liver Transplant Registry. Mortality and retransplantation. 2012. http://www.eltr.org/spip.php?article188. Accessed 27 Aug 2012.
61. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334:693–9.
62. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19(3):329–38.
63. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology. 2001;33(6):1394–403.
64. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol. 2009;10:35–43.
65. Ravaioli M, Ercolani G, Neri F, Cescon M, Stacchini G, Del Gaudio M, Cucchetti A, Pinna AD. Liver transplantation for hepatic tumors: a systematic review. World J Gastroenterol. 2014;20(18):5345–52.
66. Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A, OLT for HCC Consensus Group. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol. 2012;13(1):e11–22.

67. Cillo U, Vitale A, Bassanello M, Boccagni P, Brolese A, Zanus G, Burra P, Fagiuoli S, Farinati F, Rugge M, D'Amico DF. Liver transplantation for the treatment of moderately or well-differentiated hepatocellular carcinoma. Ann Surg. 2004;239:150–9.
68. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33(2):464–70.
69. OPTN – Organ Procurement and Transplantation policy 3.6. Liver transplant candidates with hepatocellular carcinoma. Updated 31 Oct 2013. Available at http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_8.pdf.
70. Cescon M, Cucchetti A, Ravaioli M, Pinna AD. Hepatocellular carcinoma locoregional therapies for patients in the waiting list. Impact on transplantability and recurrence rate. J Hepatol. 2013;58:609–18.
71. European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56(4):908–43.
72. Cucchetti A, Vitale A, Del Gaudio M, Ravaioli M, Ercolani G, Cescon M, Zanello M, Morelli MC, Cillo U, Grazi GL, Pinna AD. Harm benefits of primary liver resection and salvage transplantation for hepatocellular carcinoma. Am J Transplant. 2010;10(3):619–27. doi:10.1111/j.1600-6143.2009.02984. Epub 2010 Jan 29. PubMed.
73. Cucchetti A, Ercolani G, Vivarelli M, Cescon M, Ravaioli M, Ramacciato G, Grazi GL, Pinna AD. Is portal hypertension a contraindication to hepatic resection? Ann Surg. 2009;250(6):922–8.
74. Fisher RA, Kulik LM, Freise CE, Lok AS, Shearon TH, Brown RS, Ghobrial RM, Fair JH, Olthoff KM, Kam I. Hepatocellular carcinoma recurrence and death following living and deceased donor liver transplantation. Am J Transplant. 2007;7:1601–8.
75. Vakili K, Pomposelli JJ, Cheah YL, Akoad M, Lewis WD, Khettry U, Gordon F, Khwaja K, Jenkins R, Pomfret EA. Living donor liver transplantation for hepatocellular carcinoma: increased recurrence but improved survival. Liver Transpl. 2009;15:1861–6 [PubMed] [DOI].
76. Zimmerman MA, Ghobrial RM, Tong MJ, Hiatt JR, Cameron AM, Hong J, Busuttil RW. Recurrence of hepatocellular carcinoma following liver transplantation: a review of preoperative and postoperative prognostic indicators. Arch Surg. 2008;143(2):182–8.
77. Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. J Hepatol. 2012;56:1181–8.
78. Jones DE, Bhala N, Burt J, Goldblatt J, Prince M, Newton JL. Four year follow up of fatigue in a geographically defined primary biliary cirrhosis patient cohort. Gut. 2006;55(4):536–41.
79. Corpechot C, Poujol-Robert A, Wendum D, Galotte M, Chretien Y, Poupon RE, et al. Biochemical markers of liver fibrosis and lymphocytic piecemeal necrosis in UDCA-treated patients with primary biliary cirrhosis. Liver Int. 2004;24:187–93.
80. Poupon R, Chazouilleres O, Balkau B, Poupon RE. Clinical and bio- chemical expression of the histopathological lesions of primary biliary cirrhosis. UDCA-PBC Group. J Hepatol. 1999;30:408–12.
81. Roll J, Boyer JL, Barry D, Klatskin G. The prognostic importance of clinical and histologic features in asymptomatic and symptomatic primary biliary cirrhosis. N Engl J Med. 1983;308:1–7.
82. European Association for the Study of the Liver. EASL clinical practice guidelines: management of cholestatic liver diseases. J Hepatol. 2009;51:237–67.
83. Locke III GR, Therneau TM, Ludwig J, Dickson ER, Lindor KD. Time course of histological progression in primary biliary cirrhosis. Hepatology. 1996;23:52–6.
84. Poupon RE, Lindor KD, Cauch-Dudek K, Dickson ER, Poupon R, Heathcote EJ. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. Gastroenterology. 1997;113:884–90.
85. Lee J, Belanger A, Joucette JT, Stanca C, Friedman S, Bach N. Transplantation trends in primary biliary cirrhosis. Clin Gastroenterol Hepatol. 2007;5:1313–5.

86. Boberg KM, Aadland E, Jahnsen J, Raknerud N, Stiris M, Bell H. Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. Scand J Gastroenterol. 1998;33(1):99–103.
87. Lindstrom L, Boberg KM, Wikman O, Friis-Liby I, Hultcrantz R, Prytz H, Sandberg-Gertzen H, Sangfelt P, Rydning A, Folvik G, Gangsoy-Kristiansen M, Danielsson A, Bergquist A. High dose ursodeoxycholic acid in primary sclerosing cholangitis does not prevent colorectal neoplasia. Aliment Pharmacol Ther. 2012;35:451–7.
88. Jorgensen KK, Lindstrom L, Cvancarova M, Castedal M, Friman S, Schrumpf E, Foss A, Isoniemi H, Nordin A, Holte K, Rasmussen A, Bergquist A, Vatn MH, Boberg KM. Colorectal neoplasia in patients with primary sclerosing cholangitis undergoing liver transplantation: a Nordic multicenter study. Scand J Gastroenterol. 2012;8–9:1021–9.
89. Wiesner RH. Liver transplantation for primary biliary cirrhosis and primary sclerosing cholangitis: predicting outcomes with natural history models. Mayo Clin Proc. 1998;73:575–88.
90. Murray-Lyon IM, Stern RB, Williams R. Controlled trial of prednisone and azathioprine in active chronic hepatitis. Lancet. 1973;1:735–7.
91. Kirk AP, Jain S, Pocock S, Thomas HC, Sherlock S. Late results of the Royal Free Hospital prospective controlled trial of prednisolone therapy in hepatitis B surface antigen negative chronic active hepatitis. Gut. 1980;21:78–83.
92. Haber BA, Erlichman J, Loomes KM. Recent advances in biliary atresia: prospects for novel therapies. Expert Opin Investig Drugs. 2008;17(12):1911–24 [Medline].
93. Drut R, Dut RM, Gomez MA, Rua EC, Lojo MM. Presence of human papillomavirus in extrahepatic biliary atresia. J Pediatr Gastroenterol Nutr. 1998;27:530–5.
94. Domiati-Saad R, Dawson DB, Margraf LR, Finegold MJ, Weinberg AG, Rogers BB. Cytomegalovirus and human herpesvirus 6, but not human papillomavirus, are present in neonatal giant cell hepatitis and extrahepatic biliary atresia. Pediatr Dev Pathol. 2000;3:367–73.
95. Starzl TE. The saga of liver replacement, with particular reference to the reciprocal influence of liver and kidney transplantation (1955–1967). J Am Coll Surg. 2002;195:587–610.
96. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. NEJM. 1996;334:693–9.
97. Olthoff KM, Merion RM, Ghobrial RM, Abecassis MM, Fair JH, Fisher RA, Freise CE, Kam I, Pruett TL, Everhart JE, Hulbert-Shearon TE, Gillespie BW, Emond JC. Outcomes of 385 adult-to-adult living donor liver transplant recipients: a report from the A2ALL Consortium. Ann Surg. 2005;242:314–23.
98. Pichlmayr R, Weimann A, Klempnauer J, Oldhafer KJ, Maschek H, Tusch G, Ringe B. Surgical treatment in proximal bile duct cancer. A single-center experience. Ann Surg. 1996;224:628–38.
99. Becker NS, Rodriguez JA, Barshes NR, O'Mahony CA, Goss JA, Aloia TA. Outcomes analysis for 280 patients with cholangiocarcinoma treated with liver transplantation over an 18-year period. J Gastrointest Surg. 2008;12:117–22.
100. Robles R, Figueras J, Turrión VS, Margarit C, Moya A, Varo E, Calleja J, Valdivieso A, Valdecasas JC, López P, Gómez M, de Vicente E, Loinaz C, Santoyo J, Fleitas M, Bernardos A, Lladó L, Ramírez P, Bueno FS, Jaurrieta E, Parrilla P. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. Ann Surg. 2004;239:265–71.
101. Urego M, Flickinger JC, Carr BI. Radiotherapy and multimodality management of cholangiocarcinoma. Int J Radiat Oncol Biol Phys. 1999;44:121–6.
102. De Vreede I, Steers JL, Burch PA, Rosen CB, Gunderson LL, Haddock MG, Burgart L, Gores GJ. Prolonged disease-free survival after orthotopic liver transplantation plus adjuvant chemoirradiation for cholangiocarcinoma. Liver Transpl. 2000;6:309–16.
103. Sudan D, DeRoover A, Chinnakotla S, Fox I, Shaw Jr B, McCashland T, Sorrell M, Tempero M, Langnas A. Radiochemotherapy and transplantation allow long-term survival for nonresectable hilar cholangiocarcinoma. Am J Transplant. 2002;2:774–9.

104. Gu J, Bai J, Shi X, Zhou J, Qiu Y, Wu Y, Jiang C, Sun X, Xu F, Zhang Y, Ding Y. Efficacy and safety of liver transplantation in patients with cholangiocarcinoma: a systematic review and meta-analysis. Int J Cancer. 2012;130:2155–63.
105. Gores GJ, Nagorney DM, Rosen CB. Cholangiocarcinoma: is transplantation an option? For whom? J Hepatol. 2007;47:455–9.
106. Lee SG, Song GW, Hwang S, Ha TY, Moon DB, Jung DH, Kim KH, Ahn CS, Kim MH, Lee SK, Sung KB, Ko GY. Surgical treatment of hilar cholangiocarcinoma in the new era: the Asan experience. Hepatobiliary Pancreat Sci. 2010;17:476–89.
107. Aoba T, Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, Nimura Y, Nagino M. Assessment of nodal status for perihilar cholangiocarcinoma: location, number, or ratio of involved nodes. Ann Surg. 2013;257:718–25.
108. Pavel M, Baudin E, Couvelard A, Krenning E, Öberg K, Steinmüller T, Anlauf M, Wiedenmann B, Salazar R. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. Neuroendocrinology. 2012;95:157–76.
109. Le Treut YP, Grégoire E, Klempnauer J, Belghiti J, Jouve E, Lerut J, Castaing D, Soubrane O, Boillot O, Mantion G, Homayounfar K, Bustamante M, Azoulay D, Wolf P, Krawczyk M, Pascher A, Suc B, Chiche L, de Urbina JO, Mejzlik V, Pascual M, Lodge JP, Gruttadauria S, Paye F, Pruvot FR, Thorban S, Foss A, Adam R. Liver transplantation for neuroendocrine tumors in Europe-results and trends in patient selection: a 213-case European liver transplant registry study. Ann Surg. 2013;257:807–15.
110. Mazzaferro V, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? J Hepatol. 2007;47:460–6.
111. Le Treut YP, Grégoire E, Belghiti J, Boillot O, Soubrane O, Mantion G, Cherqui D, Castaing D, Ruszniewski P, Wolf P, Paye F, Salame E, Muscari F, Pruvot FR, Baulieux J. Predictors of long-term survival after liver transplantation for metastatic endocrine tumors: an 85-case French multicentric report. Am J Transplant. 2008;8:1205–13.
112. Gedaly R, Daily MF, Davenport D, McHugh PP, Koch A, Angulo P, Hundley JC. Liver transplantation for the treatment of liver metastases from neuroendocrine tumors: an analysis of the UNOS database. Arch Surg. 2011;146:953–8.
113. Hagness M, Foss A, Line PD, Scholz T, Jørgensen PF, Fosby B, Boberg KM, Mathisen O, Gladhaug IP, Egge TS, Solberg S, Hausken J, Dueland S. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg. 2013;257:800–6.
114. Cruz Jr RJ, Ranganathan S, Mazariegos G, Soltys K, Nayyar N, Sun Q, Bond G, Shaw PH, Haberman K, Krishnamurti L, Marsh JW, Humar A, Sindhi R. Analysis of national and single-center incidence and survival after liver transplantation for hepatoblastoma: new trends and future opportunities. Surgery. 2013;153:150–9.
115. Ercolani G, Grazi GL, Pinna AD. Liver transplantation for benign hepatic tumors: a systematic review. Dig Surg. 2010;27:68–75.
116. Mehrabi A, Kashfi A, Fonouni H, Schemmer P, Schmied BM, Hallscheidt P, Schirmacher P, Weitz J, Friess H, Buchler MW, Schmidt J. Primary malignant hepatic epithelioid hemangioendothelioma: a comprehensive review of the literature with emphasis on the surgical therapy. Cancer. 2006;107:2108–21.
117. Grossman EJ, Millis JM. Liver transplantation for non-hepatocellular carcinoma malignancy: indications, limitations, and analysis of the current literature. Liver Transpl. 2010;16:930–42.
118. Schwartz ME, Roayaie S, Konstadoulakis MM, Gomatos IP, Miller CM. The Mount Sinai experience with orthotopic liver transplantation for benign tumors: brief report and literature review: case reports. Transpl Proc. 2008;40:1759–62.
119. Dimick JB, Cowan JA, Knol JA, et al. Hepatic resection in the United States: indications, outcomes, and hospital procedural volumes from a nationally representative database. Arch Surg. 2003;138:185–91.
120. UNOS database, based on OPTN data as of May 15th, 2009 (www.unos.org).

121. ELTR database, update to December 31st, 2008 (www.eltr.org).
122. Everson GT, Taylor MR, Doctor RB. Polycystic disease of the liver. Hepatology. 2004;40:774–82.
123. Cavallari G, Nardo B, Montalti R, et al. Combined liver-kidney transplantation: experience at Bologna's transplant center. Transpl Proc. 2004;36:541–2.
124. Lerut J, Ciccarelli O, Rutgers M, et al. Liver transplantation with preservation of the inferior vena cava in case of symptomatic adult polycystic disease. Transpl Int. 2005;18:513–8.
125. Ueno T, Barri Y, Netto G, et al. Liver and kidney transplantation for polycystic liver and kidney-renal function and outcome. Transplantation. 2006;82:501–7.
126. Kirchner G, Rifai K, Cantz T, et al. Outcome and quality of life in patients with polycystic liver disease after liver or combined liver-kidney transplantation. Liver Transpl. 2006;12:1268–77.
127. Rosenberg L. The risk of liver neoplasm in relation to combined oral contraceptives use. Contraception. 1991;43(6):643–52.
128. Cho SW, Marsh JW, Steel J, et al. Surgical management of hepatocellular adenoma: take it or leave it? Ann Surg Oncol. 2008;15:2795–803.
129. Dokmak S, Paradis V, Vilgrain V, et al. A single center surgical experience of 122 patients with single and multiple hepatocellular adenomas. Gastroenterology. 2009;137(5): 1698–705.
130. Flejou JF, Barge J, Menu Y, et al. Liver adenomatosis. An entity distinct from liver adenoma? Gastroenterology. 1985;89:1132–8.
131. Cliché L, Dao T, Salamè E, et al. Liver adenomatosis: reappraisal, diagnosis, and surgical management. Ann Surg. 2000;231:74–81.
132. Vetelainen R, Erdogan D, De Graaf W, et al. Liver adenomatosis: re-evaluation of aetiology and management. Liver Int. 2008;28(4):499–508.
133. Bioulac-Sage P, Laumonier H, Laurent C, Blanc JF, Balabaud C. Benign and malignant vascular tumors of the liver in adults. Sem Liv Dis. 2008;28:302–14.
134. Ferraz A, Sette M, Maia M, et al. Liver transplant for the treatment of giant hepatic hemangioma. Liver Transpl. 2004;10:1436–7.
135. Todani T, Watanabe Y, Narusue M, Tabuchi K, Okajima K. Congenital bile ducts cysts: classification, operative procedures and review of thirty-seven cases, including cancer arising from choledochal cyst. Am J Surg. 1977;134:263–9.
136. Habib S, Shakil O, Couto O, et al. Caroli's disease and orthotopic liver transplantation. Liver Transpl. 2006;12:416–21.
137. De Kerckhove L, De Meyer M, Verbaandert C, et al. The place of liver transplantation in Caroli's disease and syndrome. Transpl Int. 2006;19:381–8.
138. Herraiz A, Torres-Quevedo R, Pallardo J. Transplante hepatico en pacientes con lesiones hepaticas benignas. Cir Esp. 2008;84:60–6.
139. Hernandez JC, Alfonso C, Gonzales L, et al. Solid mesenchymal hamartoma in an adult: a case report. J Clin Pathol. 2006;59:542–5.
140. Bresson-Hadni S, Koch S, Miguet JP, et al. Indications and results of liver transplantation for echinococcus alveolar infection. Lang Arch Surg. 2003;388:231–8.

Liver Procurement

7

Alessandro Cucchetti and Chiara Zanfi

7.1 Donor Evaluation and Management

There are very few absolute contraindications for abdominal organ donation, which can be summarized in the short form CHUMP: (1) Creutzfeldt-Jakob disease, (2) active HIV infection, (3) uncontrolled donor sepsis, (4) history of melanoma or other malignancy that poses a risk for transmission regardless of the apparent disease-free period, and (5) past history of non-curable malignancy (curable malignancy such as localized small kidney tumors, localized prostate cancer, localized colon malignancy >5 years previously may be considered after careful risk/benefit assessment). (Please see also Chaps. 4 and 5.)

Donors with known infections affecting organs not specifically considered for donation (e.g., a liver donor suffering from pneumonia) can be suitable for donation; in addition, children who died as a consequence of bacterial meningitis (*Haemophilus influenzae* or *Neisseria meningitidis*) can also be considered for donation if the bacteria and its sensitivity are known before liver procurement. Prolonged organ ischemia related to severe hypotension or cardiac arrest can represent a contraindication to donation; however, organ donation after circulatory death (DCD) is currently endorsed by the World Health Organization and is currently practiced worldwide, as a consequence of the chronic shortage of donors [1]. The 1995 Maastricht classification (updated in 2003) defines DCD categories according to the circumstances of the donor's death and is detailed in Table 7.1. To date, the

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Table 7.1 Definition of donor after cardiac death based on 2003 Maastricht classification (updated in 2003)

Category	Description
I	*Dead on arrival*: corneas, heart valves, skin, bone, etc., can be recovered since there are no immediate time constraints to minimize tissue injury and there is no requirement for a precisely timed approach to tissue recovery
II	*Unsuccessful resuscitation*: patients who suffered a cardiac arrest outside the hospital and underwent unsuccessful cardiopulmonary resuscitation (CPR). Following declaration of death, CPR is continued until the transplant team arrival
III	*Awaiting cardiac arrest following withdrawal of care*: after the consent of the donor family, organs may be recovered after death is declared from patients with irreversible brain injury or respiratory failure in whom treatment is withdrawn
IV	*Cardiac arrest after brain death*: a consented brain dead donor has a cardiac arrest before scheduled organ recovery
V	*Cardiac arrest in a hospital patient*: like category II originating in hospital

majority of DCD donors in Europe and the United States are type II and III; in Japan, where brain death remains culturally unpopular because not permitted until very recently, DCD is the predominant form of organ donation [1].

In addition to these general criteria, there are organ-specific criteria for guiding the acceptance of a liver for transplantation. A history of hepatitis or alcoholism is certainly a warning sign, but both livers from HBsAg-positive and/or HCV-positive donors are currently used worldwide, and suitability for transplant must be judged on a case-by-case basis [2–4]. In general, in the case of a marginal liver donor, the intraoperative assessment by the donor surgeon, in addition to liver biopsy pathological evaluation, is the best single piece of information. A 1.5-cm^2 subcapsular wedge or 2.0-cm-long needle core biopsy from the anterior inferior edge of the liver is advocated in the literature for various processes; a summary of pathological findings in association with suitability of the liver donor for transplant is reported in Table 7.2 [5].

Once these aspects have been taken into account, the transplant team can start the liver procurement.

7.2 Technical Aspects of Liver Procurement

There are fundamentally two techniques for liver procurement: the traditional standard technique developed by Starzl and the rapid en bloc technique. The standard technique for procurement of the liver (and pancreas) advocates the use of more extensive dissection of the vasculature of abdominal organs prior to cross-clamping. This method has been criticized as being time-consuming and potentially adversely affecting organs, mainly the liver. In addition, a complete dissection of the porta hepatis, and of the pancreas in the case of multiorgan donors, cannot be possible when recovering the liver from hemodynamically unstable donors [6, 7]. A rapid en bloc technique was developed in the mid-1990s to overcome these aspects. For both

Table 7.2 Features affecting acceptability of liver graft

Pathological finding	Acceptable	Unacceptable
Macrovesicular steatosis	<30 %	≥60 %
Microvesicular steatosis	Any degree	N/A
Fibrosis	Stage 1: mild fibrosis, enlargement of hepatic portal as a result of fibrosis	Stage 3: severe fibrosis with many bridges of fibrosis that link up portal and central areas of the liver
	Stage 2: moderate fibrosis, extending out from the portal areas with rare bridges between portal areas	Stage 4: cirrhosis
Viral hepatitis activity	Grade <5 (Ishak/Knodell)	Grade ≥5 (Ishak/Knodell)
Presence of granulomas	Fibrotic/calcified granulomas	Active granulomas, caseating or noncaseating
Necrosis	<10 %	≥10 %

techniques, excellent exposure is achieved through a complete midline sternal-splitting and abdominal incision.

7.2.1 Standard Technique

A midline laparotomy from the xyphoid to the pubis is performed and the round ligament divided. The intra-abdominal organs are explored to check for eventual malignancies, and the quality of the liver is assessed (Table 7.2): in the absence of contraindications for a transplant, a sternotomy can be performed. Of note, in the presence of prior heart surgery, the complete warm dissection should be made prior to the sternotomy. It is also prudential to isolate and encircle the aorta prior to sternotomy in order to be ready to cannulate in the event of cardiac arrest/injury at thoracotomy. A blunt dissection behind the sternum just below the jugular notch should be performed until the fingertip can be placed retrosternal around the jugular notch. The sternotomy is then performed in a cranial to caudal direction with the sternum saw to avoid left innominate vein injury.

The division of the left triangular ligament allows the mobilization of the left lateral segments of the liver and the exposure of the supraceliac aorta just below the diaphragm to be encircled. The division of the falciform ligament up to the suprahepatic inferior vena cava (IVC) provides more mobility of the liver, necessary when the IVC must be divided from a cardiac graft. Before starting the dissection of the hepatoduodenal ligament, the hepatogastric ligament must be inspected by dividing the lesser omentum. This ligament is usually very thin and transparent so that any replaced or accessory left hepatic artery should be easily visible. In addition, palpation of the ventral border of the foramen of Winslow makes it possible to identify a

possible accessory or replaced right hepatic artery. Variations in the hepatic arterial supply can complicate the hilar dissection in up to one third of donors.

The hilar structures of the liver are then dissected free; the common bile duct (CBD) is dissected on the level of the edge of the second duodenal portion after opening of the peritoneum and visualization of the duct. In difficult cases, due to a high BMI, following the cystic duct out of the gall bladder can help to identify the CBD. The CBD should be encircled from the lateral border of the hepatoduodenal ligament in order to avoid injury of the portal vein. The CBD and the gallbladder are opened and flushed with normosaline solution. The origins of the gastroduodenal, gastric, and splenic arteries are then identified and encircled and, in the case of liver only procurement, will be taped just before cross-clamping in order to increase flushing through the hepatic artery to the liver.

The aorta can be isolated by two approaches. One approach requires mobilization of the right colon on top of Gerota's fascia and should be extended into a Kocher maneuver to uncover both the inferior vena cava and the abdominal aorta; the other approach is performed by opening the root of the mesentery from the Treitz fascia, along the margin of the duodenum until visualization of the right iliac vessels and ureter is achieved. The inferior mesenteric artery can be tied and divided, and the abdominal aorta, just 2–3 cm above the bifurcation, isolated and encircled. The lumbar arteries could be either tied or clipped and then cut in order to provide mobility of the aorta and facilitate the cannulation. Two umbilical tapes are placed around the dissected segment of the aorta and secured by clamps and will be used to secure aortic cannulae to the vessel. The inferior mesenteric vein (IMV) is most commonly used for access into the portal system by ligating the distal part of it but leaving it uncut to retract the vein with a mosquito clamp. Another tie is then placed around the cranial portion of the vein, using it for occlusion of the vein by retracting it while a partial incision of the vein is performed. The portal cannula can be inserted into the IMV while the tension of the occluding tie is decreased before tying it around the vein and inserted cannula. At this point, 30,000-IU heparin should be given to prevent the blood from clotting after the cross-clamping. Once these preliminary procedures have been completed, the aortic cannulae (20-F armed cannulae) can be inserted into the distal abdominal aorta and secured with the umbilical tapes.

The subdiaphragmatic aorta is now clamped (cross-clamp), and cold preservation solution is then rapidly infused through the aortic and portal cannulae; the liver flow is decompressed by dividing the inferior vena cava in the chest. The abdomen is filled with water and ice. The choice of solution for infusion and its amount varies from center to center. The quality of the flush can be assessed by evaluating the outflow of the supradiaphragmatic IVC which should become more transparent with time as the blood in the abdominal organs is replaced by the preservation solution. After the flush is completed, some of the ice is removed from the abdomen to allow the cold dissection of the structures.

The gastroduodenal, gastric, and splenic arteries can now be divided. Just below the gastroduodenal artery, the portal vein can be found and can be followed back, if pancreas procurement is not performed, by dividing the head of the pancreas. The

cannulae in the IMV can now be removed, the splenic vein ligated and divided, and the venous cannulae replaced in the superior mesenteric vein once it is divided from its distal branches. The superior mesenteric artery (SMA) can now be found in the retro-pancreatic laminae and should be ligated, secured to a clamp and divided in order to find the aortic plane by following back the SMA. This dissection must be made on the left side of the SMA in order to avoid damage to a possible replaced or accessory right hepatic artery. The renal arteries are usually just below the SMA. They should be visualized before the suprarenal aorta is divided. This section must be made in 45°, first looking for ostia of accessory renal arteries before performing complete separation of the aorta. By following back the splenic and gastric arteries, the celiac trunk can be visualized. The aorta must now be divided just below the diaphragm, obtaining a patch containing the celiac trunk and the origin of the mesenteric artery.

At this time point, a finger is placed in the supradiaphragmatic IVC helping to identify it while the diaphragm is cut. A portion of the diaphragm should be kept with the liver to ensure that this gross and fast dissection does not damage the organ. The diaphragm is cut to the right, and the incision is then continued between the right kidney and the liver, usually dividing the adrenal gland which is a good sign that none of the adjacent organs are damaged. The location for division of the infrahepatic IVC depends on the renal veins. These are identified on both sides, and the IVC can be safely divided on the virtual line about 1 cm above the renal veins. The only structures now holding the liver in the abdomen are the diaphragmatic pillars. By keeping the liver to the right thoracic cavity and holding the aortic patch, the resected IVC, and the portal vein with its cannulae, the liver removal can be completed by cutting the diaphragmatic muscles. The liver is freed and taken out of the abdomen. A further perfusion with cool preservation solution should be performed on the back table before packing the liver in the transportation box usually with 1 l of preservation solution. The liver can now be packed in the transportation box.

7.2.2 Rapid Technique

The standard technique of liver procurement often requires 2 or more hours of preliminary dissection of the hepatic structures. This manipulation could inadvertently produce warm ischemic injury to the liver by interfering intermittently with either portal or hepatic artery flow and could increase the risk of injury to vital structures, especially an anomalous arterial supply to the liver. In addition, such a prolonged procedure could not be tolerated in an unstable donor and is not always conducive to collaboration among different transplant teams. The “rapid” technique requires no preliminary dissection except for encirclement of the aorta just below the diaphragm and cannulation of the inferior mesenteric vein and distal aorta [6, 7]. Once the aorta is cross-clamped, cold infusion is begun through both cannulae. The hilar dissection can then be completed safely in the cold and rapidly in a bloodless field: cold dissection is the same as the standard technique. The preparatory steps by the liver procurement teams require only 15–20 min. The “rapid” technique of organ

procurement can increase the practicality of harvesting under various adverse circumstances, for example, in DCD donors.

In DCD donors a 20-French chest tube is used for cannulation of the femoral artery and a 28-French tube for cannulation of the femoral vein. Phentolamine 10–20 mg is administered to produce vasodilatation, and 30,000 units of heparin is administered as previously described. Following declaration of death, and a 5-min waiting time (please see introduction section), the femoral artery is flushed with preservation solution and the femoral vein opened to decompress the venous system. The surgical procedure then starts with a median sternotomy and midline laparotomy; the pericardium is opened and the thoracic aorta clamped. The abdominal organs can now be removed with an en block dissection by dividing the diaphragmatic attachments and dissecting in the retroperitoneal space; alternatively, a cold standard dissection can be performed.

References

1. Morrissey PE, Monaco AP. Donation after circulatory death: current practices, ongoing challenges, and potential improvements. Transplantation. 2014;97(3):258–64.
2. Yu S, Yu J, Zhang W, Cheng L, Ye Y, Geng L, Yu Z, Yan S, Wu L, Wang W, Zheng S. Safe use of liver grafts from hepatitis B surface antigen positive donors in liver transplantation. J Hepatol. 2014. doi:10.1016/j.jhep.2014.05.003. pii: S0168-8278(14)00312-2.
3. Loggi E, Micco L, Ercolani G, Cucchetti A, Bihl FK, Grazi GL, Gitto S, Bontadini A, Bernardi M, Grossi P, Costa AN, Pinna AD, Brander C, Andreone P. Liver transplantation from hepatitis B surface antigen positive donors: a safe way to expand the donor pool. J Hepatol. 2012;56(3):579–85.
4. Ballarin R, Cucchetti A, Spaggiari M, Montalti R, Di Benedetto F, Nadalin S, Troisi RI, Valmasoni M, Longo C, De Ruvo N, Cautero N, Cillo U, Pinna AD, Burra P, Gerunda GE. Long-term follow-up and outcome of liver transplantation from anti-hepatitis C virus-positive donors: a European multicentric case-control study. Transplantation. 2011;91(11):1265–72.
5. Melin C, Miick R, Young NA, Ortiz J, Balasubramanian M. Approach to intraoperative consultation for donor liver biopsies. Arch Pathol Lab Med. 2013;137:270–4.
6. Pinna AD, Dodson FS, Smith CV, Furukawa H, Sugitani A, Fung JJ, Corry RJ. Rapid en bloc technique for liver and pancreas procurement. Transplant Proc. 1997;29(1–2):647–8.
7. Imagawa DK, Olthoff KM, Yersiz H, Shackleton CR, Colquhoun SD, Shaked A, Busuttil RW. Rapid en bloc technique for pancreas-liver procurement. Improved early liver function. Transplantation. 1996;61(11):1605–9.

Orthotopic Liver Transplantation

8

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8.1 Standard (Conventional) Technique of Liver Transplantation

The standard technique of whole liver transplantation (LT) was originally described by Starzl, and it has remained substantially unchanged over time [1, 2]. The conventional technique includes (1) the removal of the native liver together with the retrohepatic inferior vena cava (IVC) and (2) the use of a venovenous bypass to maintain the venous flow from the inferior and superior vena cava districts and the shunt of the portal system draining the abdominal viscera into the systemic circulation.

Before proceeding with the abdominal incision, the venous accesses for the venovenous bypass are prepared with a surgical or a percutaneous approach. In the first case, the saphenous and the ipsilateral axillary vein are exposed and freed. In the second case, the femoral vein and the internal jugular veins are cannulated with large-size catheters.

A J-shaped incision (right subcostal incision extended to the median line up to the xiphoid cartilage) is performed. Alternatively, this incision can be extended to the left subcostal line (the so-called "Mercedes" incision). The right and left costal margins are retracted with a wide retractor. The J-shaped incision usually leads to a lower rate of abdominal wall complications compared to the "Mercedes" incision [3], but it is sometimes insufficient in providing optimal visceral exposure.

The umbilical ligament is ligated and divided, paying attention to the frequent presence of a patent umbilical vein in cases of marked portal hypertension. The falciform ligament is divided with electrocautery as far as the suprahepatic hilum.

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The dissection of the hepatoduodenal ligament starts with division of the peritoneal layer close to the liver. This tissue often contains enlarged lymphatic vessels, whose division is preferably performed after ligatures rather than with the electrocautery in order to reduce the possibility of postoperative ascites. The hepatic artery (HA) is isolated and divided, preferably at the level of right and left branches in order to keep these vessels as long as possible for the subsequent anastomosis. The main bile duct is divided; after this step, it is possible to further isolate the HA by dividing the pyloric artery and the gastroduodenal artery (GDA). These maneuvers are especially useful when the patient is hemodynamically stable, an acceptably short ischemia time is anticipated, and sufficient hemostasis can be achieved. The purpose is to reduce the arterial ischemia time because the HA stump is already prepared for the subsequent anastomosis, which is more commonly performed at the outlet of the GDA from the common hepatic artery (CHA). When the above favorable circumstances are not present, the HA is fully prepared after portal revascularization.

The arterial periadventitial tissue should be left intact to avoid vasospasm and possible arterial dissection.

The portal trunk is isolated by freeing it from the abundant lymphatic tissue, which surrounds the vessel anteriorly and posteriorly, and should be ligated rather than electrocoagulated, especially in cases of elevated portal hypertension.

The liver is then mobilized by dividing the left and right triangular ligaments, which are often rich in dilated veins, making it necessary to use the electrocautery or ligatures with careful control of the bleeding. The mobilization of the left lobe of the liver is sometimes difficult due to its hypertrophy and its close contact with the spleen.

The right adrenal gland is detached from the posterior surface of the liver; to avoid bleeding from this gland, which is very fragile and strictly adherent to the liver, it is often necessary to ligate and divide it, using sutures for better control of bleeding. The above maneuvers allow exposure of the right posterior aspect of the retrohepatic IVC. On the left side, the lesser sac is divided, and the posterior peritoneal tissue covering the vena cava is opened below the caudate lobe, using ligatures or electrocoagulation. These maneuvers permit the exposure of the left posterior aspect of the infrahepatic vena cava.

The suprahepatic inferior vena cava is freed as much as possible from the diaphragm in order to obtain a sufficiently long stump for the upper caval anastomosis, and then it is encircled and taped. Inferiorly, the infrahepatic vena cava is isolated and taped, this maneuver being facilitated by the division of one or more inferior accessory hepatic veins.

As mentioned above, the original standard technique of LT includes the use of the venovenous bypass. In fact, some groups routinely perform LT without bypass, which is required only exceptionally in their experience [4]. Avoidance of bypass is possible when the anesthesiology team is very experienced and able to maintain the hemodynamic stability during the anhepatic phase through an accurate balance of intravenous fluid infusion and vasopressors.

Together with preservation of an adequate hemodynamic state, the venovenous bypass prevents from splanchnic and caval sequestration and renal failure due to

blood stagnation [5]. It is constructed with the Griffith circuit and a Bio-Pump, which collects the blood coming from one catheter inserted in the iliac vein (through the saphenous or the femoral vein) and one catheter inserted into the portal vein trunk. The blood is then pumped to the superior vena cava circulation through the axillary vein or the internal jugular vein with a velocity ranging from 1 to 2–2.5 L/ min.

After preparation and starting of the bypass, the recipient vena cava is cross-clamped below the liver with a DeBakey clamp and above the liver with a large, curved clamp, robust enough to include a portion of the diaphragm containing the diaphragmatic veins.

The suprahepatic IVC is divided inside the liver, at the level of the stumps of the major hepatic veins, for subsequent modeling of a large orifice for the anastomosis. The inferior caval stump is obtained by sectioning it around 1 cm above the inferior clamp. The native liver is removed, and hemostasis of the retrohepatic space, at the level of the middle diaphragmatic line, is achieved with sutures given the constant tendency to bleeding of this area.

The liver graft is then removed from the cooler and placed in the operation field, wrapped in a laparotomic gauze soaked in cold saline solution.

The upper caval anastomosis is performed by positioning of stay sutures on the right and left corners and with a running, preferably everting, 3/0 or 4/0 PROLENE® suture.

The lower vena cava anastomosis is performed with a 4/0 PROLENE® running suture. Simultaneously, the graft is washed with 700–1,000 mL of cold (4 °C) saline, Ringer or albumin-containing solution through the catheter placed in the portal vein during organ retrieval, with the aim of eliminating the preservation solution contained in the liver and of preventing air embolism. The preservation solution is often rich in potassium, whose sudden elevation in the blood after graft reperfusion could cause arrhythmias or cardiac arrest.

The catheter placed in the recipient portal vein for the bypass is removed, and an end-to-end portal vein anastomosis is performed, after positioning of stay sutures, with an over-and-over, or everting, 5/0 or 6/0 PROLENE® running suture. It is preferable not to tie the suture tightly, but to leave about 0.5–1 cm of loose tie (the so-called growth factor [6]) because the portal vein wall is often subjected to some degree of distension after portal vein unclamping, especially in the case of elevated portal hypertension. A tight tie could determine portal vein stricture (Fig. 8.1).

The sequence of vascular clamp release is variable, but usually the suprahepatic vena cava is unclamped first, followed by the portal vein and lower IVC. At this stage, the anesthesiology team must keep the central pressure low in order to avoid an excessive cardiac preload that could affect adequate venous outflow from the graft.

The arterial anastomosis is usually performed in an end-to-end fashion between the branch patch obtained between the recipient CHA and the origin of the GDA and the CHA of the donor liver. On the recipient side, the arterial stump obtained by extending the orifice of the CHA to the GDA is usually as large as possible, and it prevents any steal phenomenon through the GDA, whose distal stump is carefully

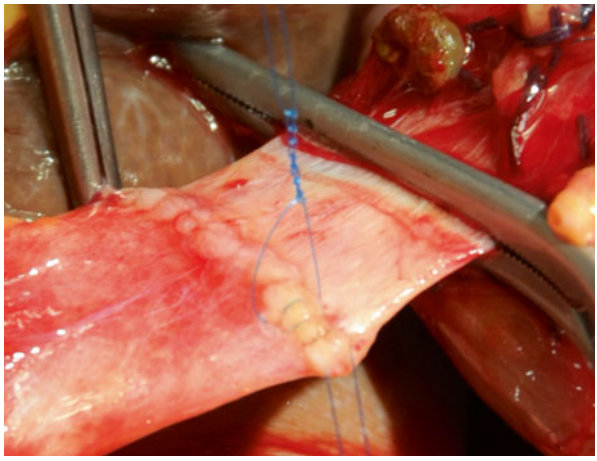

Fig. 8.1 Completion of end-to-end portal vein anastomosis in orthotopic liver transplantation. The running suture was not fully tied, leaving a loose tract of the thread ("growth factor") to allow distension of the anastomosis after reperfusion, thus preventing portal vein stricture

sutured. At the same time, using the donor CHA normally allows a short and straight reconstruction. Performing the anastomosis on the donor celiac trunk has the theoretical advantage of a wider stump on the donor side, but it usually determines an excessive length of the post-anastomotic arterial axis, with the consequent risk of kinking. In addition, the donor celiac artery, and even more the Carrel patch, is much more frequently involved by atherosclerotic plaque than the CHA in the case of older donors. Depending on the size of the arteries, the anastomosis is usually performed with 6/0, 7/0, or 8/0 PROLENE® sutures, which can be a running or an interrupted one. Wider arterial orifices, especially on the donor side, can be obtained by creating oblique stumps.

Other recipient sites for arterial reconstruction can be the proper hepatic artery, especially at the bifurcation of the right and left branches, or an accessory/replaced right hepatic artery (aRHA) from the superior mesenteric artery (SMA) in the case of absent or small CHA, or the splenic artery (SA) close to its origin from the aorta in the case of unsuitability of any HA [7]. In this latter case, the reconstruction may require an interposition donor arterial graft due to the distance between SA and CHA, and the anastomosis can be performed in an end-to-end or an end-to-side fashion. A careful evaluation of possible consequences is necessary when using the recipient SA, because an end-to-end anastomosis requires the interruption of arterial flow to the spleen through the SA itself, while an end-to-side anastomosis could determine a steal phenomenon by the spleen.

When the recipient HA is unsuitable, as in the case of very small size or dissection due to surgical maneuvers, or previous intra-arterial treatments, arterial revascularization can also be obtained by interposing an arterial vascular graft between the infrarenal aorta, or the supraceliac aorta [8], and the HA. In such cases, a donor iliac artery is more frequently used as an interposition graft. The recipient aorta is isolated and clamped longitudinally, and an end-to-side anastomosis is performed first with the vascular graft, usually with a 5/0 or 6/0 PROLENE® running suture. If the infrarenal aorta is used, the arterial graft is then passed through the transverse

mesocolon, behind the stomach, and in front of the pancreas, for the subsequent end-to-end anastomosis with the donor HA.

In around 20–30 % of cases, the liver graft presents with arterial anomalies, more frequently consisting in an aRHA (from the SMA), an accessory left hepatic artery (aLHA, from the left gastric artery), or a combination of the above.

In the case of an aRHA, it is usually reconstructed in an end-to-end fashion with the donor GDA (Fig. 8.2). Alternatively, it can be reconstructed on the stump of the donor SA. The aRHA can be preserved also by creating a single donor arterial stump with an end-to-end anastomosis between the celiac artery and the SMA (the so-called mesenteric conduit), which is subsequently anastomosed to the recipient HA. However, this technique may lead to an excessively long arterial tract.

In the case of an aLHA, its preservation requires a reconstruction between the recipient HA and the donor celiac artery, with the already-mentioned risk of kinking. In most cases, the aLHA is very small and can simply be ligated. If the aLHA is very large, after HA reconstruction the entire arterial axis is rechecked for its length after positioning of the aLHA deeply below the left lobe of the liver. If kinking is visible, the HA can be shortened, with a subsequent end-to-end anastomosis (Fig. 8.3).

In general, when multiple reconstructions are anticipated, the arterial backflow through the stumps of accessory arteries should be checked, and an intraoperative color Doppler ultrasound examination should be performed in order to quantify the parameters of perfusion of areas vascularized by accessory arteries. If a pulsate backflow is present and the left lateral segment or the right posterior segments

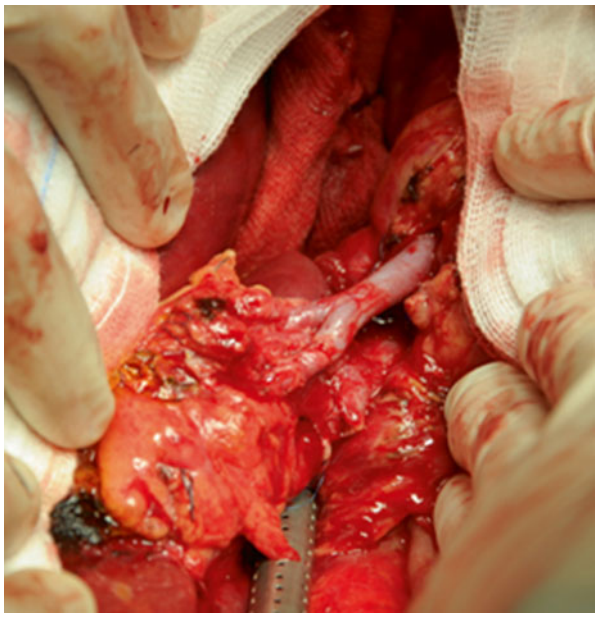

Fig. 8.2 Reconstruction of a donor accessory right hepatic artery on the stump of the donor gastroduodenal artery

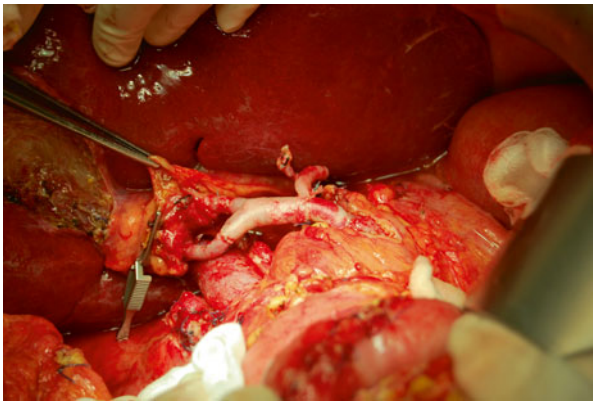

Fig. 8.3 Liver graft with a common hepatic artery and two accessory arteries (*right* and *left*). In this case, the accessory right hepatic artery was reconstructed on the donor gastroduodenal artery after anastomosis between the recipient common hepatic artery and the donor celiac artery. However, the entire arterial tract appeared too long and at risk of kinking; thus, the donor common hepatic artery was shortened with a subsequent end-to-end anastomosis

display a normal arterial flow pattern, the reconstruction of accessory arteries is not strictly necessary.

In our early experience, grafts from older donors, the use of interposition arterial grafts, multiple arterial reconstructions, and the absence of antiplatelet prophylaxis were predictors of arterial complications [9]. However, in a more recent experience, only interposition grafts and HA anatomical variations remained factors independently related to HA thrombosis after LT [10].

When a portal vein thrombosis is present in the recipient, different types of portal vein reconstruction have been suggested and will be discussed in a dedicated section. In these cases, a completely normal or physiological portal flow might not be restored. Thus, completion of the HA reconstruction is advisable before portal reperfusion, with subsequent simultaneous arterial and portal reperfusion. This strategy may lead to a slightly longer warm ischemia time, but it ensures adequate graft revascularization.

In general, there is no absolute agreement on the best sequence of graft reperfusion, which can be retrograde (by releasing the caval clamp first), portal, or arterial. However, initial portal vein revascularization is certainly the most frequently adopted [11, 12].

The biliary reconstruction is usually performed between the donor and recipient main bile ducts in an end-to-end fashion, using a 5/0 or 6/0 PDS® running or interrupted suture.

The bile duct stumps must be well vascularized, and in this sense electrocauterization should be avoided around these elements. Ideally, the sectioning of the donor and recipient bile ducts is best performed above and below the junction of the cystic ducts, respectively, provided that the two bile duct stumps are long enough to be anastomosed without stretching. These sectioning sites guarantee good

vascularization and eliminate the risk of posttransplant dilation of a retained cystic duct, which could be progressively filled with mucus and compress the bile duct, causing its stricture.

A T-tube can be inserted into the bile duct before completion of the anastomosis of the anterior walls. The upper and lower short branches of the tube are placed across the anastomosis and in the distal bile duct, respectively, while the long branch is brought out through the recipient bile duct wall around 2 cm distally to the anastomosis and then through the abdominal wall. The T-tube has the advantage of allowing intra- and postoperative cholangiography, maintaining a patent lumen in the case of tendency to stricture for different causes (technical, vascular), and draining the bile outside in the case of bile leaks. The main disadvantage lies in the possibility of bile leaks during T-tube removal.

At present, there is no evidence of superiority or inferiority of biliary anastomosis performed with or without a T-tube [13].

When there is a discrepancy in the size of bile ducts, end-to-end anastomosis can still be performed in many cases, especially when the recipient bile duct is larger. Otherwise, a side-to-side or end-to-side anastomosis or a choledochojejunostomy can be carried out. The latter could represent the only possible bile duct reconstruction in particular circumstances, such as previous biliary procedures, retransplantation, marked bile duct discrepancy, or sclerosing cholangitis. Usually the bilioenteric anastomosis is performed in an end-to-side fashion between the donor common hepatic duct (or choledocus) and a Roux-en-Y jejunal loop, following the conventional principles of biliary surgery. The anastomosis is usually performed with a running or interrupted 5/0 or 6/0 PDS® suture. A small urethral or infant feeding tube can be placed across the anastomosis, either as a short disposable catheter or as a Witzel-tunneled catheter brought out through the jejunal loop around 15 cm distally from the anastomosis.

At the end of the procedure, two suction drains or tubes are normally placed in the right subdiaphragmatic space and below the hilum of the liver graft.

8.2 Liver Transplantation with Preservation of the Inferior Vena Cava

LT with preservation of the recipient vena cava has been proposed as an alternative to the conventional LT technique with the main advantage of maintaining the caval flow throughout the procedure [14], thus avoiding the use of the venovenous bypass.

The first stage of the procedure is identical to the conventional technique, with preparation of the hepatoduodenal ligament. Bile duct and HA are divided, while the portal trunk is left intact to preserve the portal flow until the late stages of the hepatectomy. The right branch of the portal vein can be ligated in order to decrease the hepatic inflow, thus reducing the bleeding from the liver parenchyma and, in some circumstances, decreasing the liver volume. This maneuver facilitates the detachment of the native liver from the retrohepatic vena cava. Alternatively, intermittent portal clamping can be used or a temporary portacaval shunt [15] can be performed.

After division of the triangular ligaments has been completed, the infrahepatic vena cava is approached from both the right and the left sides. On the left side, the lesser sac is opened through ligatures, electrocautery, or other devices. The peritoneum surrounding the infrahepatic vena cava is opened, and left-sided small accessory hepatic veins are ligated, or sutured, and divided. The Spiegel lobe can be raised, and at least one large hepatic vein draining the caudate lobe is encountered. Its division might be difficult in the case of caudate lobe hypertrophy.

On the right side, accessory hepatic veins are also divided in a caudo-cranial direction. The dorsal ligament of the vena cava is taken down, so that the liver can be raised and rotated to the left side, allowing exposure of the entire anterior surface of the infrahepatic vena cava up to the outlet of the three major hepatic veins.

At this point, the portal vein can be clamped and divided. The right, middle, and left hepatic veins are clamped with a robust clamp, and the native liver is removed.

There are different techniques of caval anastomosis. The one initially described in humans by Tzakis et al. [14] is known as the "piggyback technique" and consists in the division of the septa between the right hepatic vein and the common trunk of the middle and left hepatic veins and between the latter two veins, thus obtaining a single, wide orifice for the anastomosis with the suprahepatic vena cava of the liver graft. When the three major hepatic veins do not lie on the same frontal plane, it is usually necessary to include a portion of the anterior caval wall into the clamp bite, and a venoplasty of the hepatic veins is performed. The anastomosis is usually performed with a running suture with a 4/0 PROLENE® stitch.

An alternative to the above technique consists in the division of the right hepatic vein with suturing of its caval side, followed by clamping of the common trunk of the middle and left hepatic veins with inclusion of a portion of the anterior surface of the vena cava. The septum of the middle and left hepatic veins is divided, and the anterior wall of the vena cava included in the clamp bite is opened transversally for at least 1 cm, so as to obtain a sufficiently wide stump. Ligature of the right branch of the portal vein is advisable before division of the right hepatic vein in order to avoid liver congestion.

Another technique of outflow reconstruction is represented by the cavo-caval anastomosis (cavocavostomy) [16, 17] (Fig. 8.4). On the recipient side, the caval orifice can be obtained by the closure of the stump of hepatic veins and the longitudinal opening of the anterior caval wall or by including the three hepatic veins and the longitudinal vena cava opening in a single stump. On the donor liver side, the stump can be formed by the suprahepatic vena cava, the suprahepatic vena cava with longitudinal opening of the caval wall, or by this longitudinal opening only, after closure of the suprahepatic vena cava orifice.

Therefore, depending on the above variations, side-to-side or end-to-side cavocavostomy can be performed.

Despite its popularity and advantages, also sustained by our randomized study reported more than 10 years ago [18], there is currently no evidence to recommend or refute the use of the piggyback method compared to the conventional technique of liver transplantation [19].

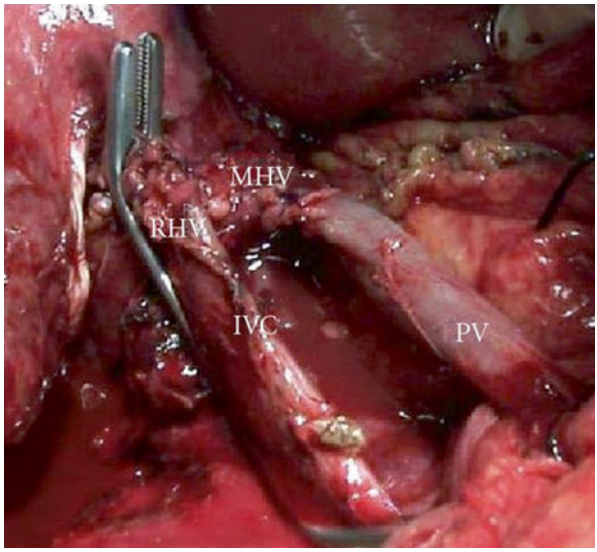

Fig. 8.4 Lateral clamping of the recipient retrohepatic vena cava. In this case, a living-donor liver transplantation was performed, and a temporary shunt was created between the portal vein and the stump of the middle and left hepatic veins with an interposition vein graft from the tissue bank. *MHV* middle hepatic, vein, *RHV* right hepatic vein, *IVC* inferior vena cava, *PV* portal vein

The portal vein anastomosis is performed as in the conventional technique. Before declamping the caval anastomosis, the liver graft is flushed with cold saline solution, Ringer solution, or albumin-containing solution so as to wash out the preservation fluid contained in the liver. The same effect can be obtained by restoring the portal flow, leaving the blood pouring from the caudal stump of the infrahepatic vena cava of the graft. At the end of the flushing, this stump is closed and the clamps on the caval and portal anastomosis are definitively removed. The arterial and biliary anastomoses are performed as with the conventional technique.

References

1. Starzl TE, Marchioro TL, von Kaulla KN, Hermann G, Brittain RS, Waddell WR. Homotransplantation of the liver in humans. Surg Gynecol Obstet. 1963;117:659–76.
2. Starzl TE, Kaupp HA, Brock DR, Lazarus RE, Johnson RV. Reconstructive problems in canine liver homotransplantation with special reference to the postoperative role of hepatic venous flow. Surg Gynecol Obstet. 1960;111:733.
3. Heisterkamp J, Marsman HA, Eker H, Metselaar HJ, Tilanus HW, Kazemier G. A J-shaped subcostal incision reduces the incidence of abdominal wall complications in liver transplantation. Liver Transpl. 2008;14:1655–8.
4. Kluger MD, Memeo R, Laurent A, Tayar C, Cherqui D. Survey of adult liver transplantation techniques (SALT): an international study of current practices in deceased donor liver transplantation. HPB. 2011;13:692–8.
5. Shaw Jr BW, Martin DJ, Marquez JM, et al. Venous bypass in clinical liver transplantation. Ann Surg. 1984;200:524–34.
6. Starzl TE, Iwatsuki S. A growth factor in fine vascular anastomoses. Surg Gynecol Obstet. 1984;159:164–6.
7. Todo S, Makowka L, Tzakis AG, et al. Hepatic artery in liver transplantation. Transpl Proc. 1987;19:2406–11.

8. Shaked A, Takill H, Busuttil RW. The use of supraceliac aorta for hepatic arterial revascularization in transplantation of the liver. Surg Gynecol Obstet. 1991;173:198–202.
9. Vivarelli M, La Barba G, Cucchetti A, Lauro A, Del Gaudio M, Ravaioli M, Grazi GL, Pinna AD. Can antiplatelet prophylaxis reduce the incidence of hepatic artery thrombosis after liver transplantation? Liver Transpl. 2007;13:651–4.
10. Cescon M, zanello M, Grazi GL, Cucchetti A, Ravaioli M, Ercolani G, Del Gaudio M, Lauro A, Morelli MC, Pinna AD. Impact of very advanced donor age on hepatic artery thrombosis after liver transplantation. Transplantation. 2011;92:439–45.
11. Millis JM, Melinek J, Csete M, Imagawa DK, Olthoff KM, Neelankata G, Braunfeld MY, Sopher MJ, Chan SM, Pregler JL, Yersiz H, Busuttil AA, Shackleton CR, Shaked A, Busuttil RW. Randomized controlled trial to evaluate flush and reperfusion techniques in liver transplantation. Transplantation. 1997;63:397–403.
12. Polak WG, Porte RJ. The sequence of revascularization in liver transplantation: it does make a difference. Liver Transpl. 2006;12:1566–70.
13. Riediger C, Müller MW, Michalski CW, Hüser N, Schuster T, Kleeff J, Friess H. T-tube or no T-tube in the reconstruction of the biliary tract during orthotopic liver transplantation: systematic review and meta-analysis. Liver Transpl. 2010;16:705–17.
14. Tzakis A, Todo S, Starzl TE. Orthotopic liver transplantation with preservation of the inferior vena cava. Ann Surg. 1989;210:649–52.
15. Belghiti J, Noun R, Sauvanet A. Temporary portocaval anastomosis with preservation of caval flow during orthotopic liver transplantation. Am J Surg. 1995;169:277–9.
16. Belghiti J, Panis Y, Sauvanet A, Gayet B, Fékété F. A new technique of side to side caval anastomosis during orthotopic hepatic transplantation without inferior vena caval occlusion. Surg Gynecol Obstet. 1992;175(3):270–2.
17. Lerut J, Gertsch P. Side-to-side cavo-cavostomy: a useful aid in “complicated” piggy-back liver transplantation. Transpl Int. 1993;6:299–301.
18. Jovine E, Mazziotti A, Grazi GL, et al. Piggy-back versus conventional technique in liver transplantation: report of a randomized trial. Transpl Int. 1997;10:109–12.
19. Gurusamy KS, Pamecha V, Davidson BR. Piggy-back graft for liver transplantation. Cochrane Database Syst Rev. 2011;(81):CD008258.

Anaesthetic and Perioperative Management for Liver Transplantation

9

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9.1 Pathophysiological Effects of Liver Disease and Preoperative Evaluation

9.1.1 Central Nervous System

Hepatic encephalopathy (HE) is a brain dysfunction caused by liver insufficiency and/or portal systemic shunt (PSS); it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma [1–3]. The pathogenesis of hepatic encephalopathy is not completely understood, but most theories implicate elevated levels of ammonia, a gut-derived neurotoxin, which is shunted to the systemic circulation from the portal system [4]. Computed tomography, magnetic resonance or other imaging techniques do not contribute to the diagnosis or to the staging of the pathology [5]. However, the risk of intracerebral haemorrhage is at least fivefold increased in this patient population [6], and the symptoms may be indistinguishable; hence, a brain scan is usually part of the diagnostic workup of patients developing HE for the first time and on clinical suspicion of other pathologies [5, 7–9].

Patients who develop fulminant hepatic failure are at risk for hepatic encephalopathy, cerebral oedema with increased intracranial pressure (ICP) and herniation. In cases of altered mental status, a head CT scan is often indicated to evaluate intracranial bleeding, herniation, the extent of cerebral oedema or both.

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9.1.2 Cardiovascular System

Patients with advanced cirrhosis present a hyperdynamic circulatory syndrome consisting in a reduction of peripheral vascular resistance and an increase in cardiac output so that they manifest arterial hypotension and tachycardia [10].

The pathophysiological background of these abnormalities has been recently identified in the arteriolar vasodilation, mainly developed in the splanchnic area, which reduces effective volaemia and provokes the compensatory activation of vasoconstrictor neurohumoral systems. Although the mechanisms leading to arterial vasodilation are not fully clarified, a pivotal role is played by an imbalance of vasoactive substances, in favour of an increased production and activity of vasodilators [11–14]. In the last decade, experimental and clinical studies have demonstrated that cirrhosis is also associated with abnormalities of cardiac function, involving both contractility and electrophysiology, which have been termed 'cirrhotic cardiomyopathy'. These abnormalities usually remain subclinical, and their significance is still under discussion. However, it is generally thought that they can be unveiled by stress conditions, such as physical exercise, bleeding, infections and major surgery. Ventricular diastolic dysfunction and electrophysiological abnormalities such as chronotropic incompetence and a prolonged QT interval also are demonstrated in cirrhotic patients [15]. Systemic conditions such as haemochromatosis (ventricular hypertrophy with increased end-diastolic and end-systolic volumes), amyloidosis (restrictive cardiomyopathy), Wilson's disease (supraventricular extrasytolic beats) and alcoholism (systolic and diastolic dysfunction) can affect liver and cardiac function [16]. The assessment and management of liver failure patients with coronary artery disease (CAD) are currently one of the most controversial areas in the field [17–19]. Many studies have revealed that CAD, both overt and occult, occurs at least as commonly in the pre-liver transplant population as it does in matched controls, and that, when present, CAD predicts a poor outcome [20, 21].

9.1.3 Pulmonary System

The pulmonary complications associated with liver disease include restrictive lung disease, intrapulmonary shunts, ventilation-perfusion abnormalities and pulmonary hypertension. The restrictive disease is the result of ascites and/or pleural effusions and frequently responds to fluid removal. Hepatopulmonary syndrome (HPS) is defined by the combination of intrapulmonary vascular dilatation (IPVD) and hypoxemia in patients with chronic liver disease or portal hypertension [22]. IPVD can cause a right to left shunt resulting in an elevated alveolar-arterial oxygen pressure gradient (A-aDO_2) and hypoxemia [23, 24].

The contrast-enhanced transthoracic echocardiography (CE-TTE) can detect a shunt and establish HPS diagnosis. In the occurrence of HPS, micro-bubbles will be visualized going from the right to the left atrium within four to six beats [24].

Portopulmonary hypertension syndrome (POHS) is defined by portal hypertension, mean pulmonary artery pressure (mPAP) >25 mmHg, pulmonary vascular resistance (PVR) >240 dyn s cm^{-5} and pulmonary artery occlusion pressure (mPAOP) <15 mmHg [22, 25].

POHS is a relatively common condition among LT candidates with a prevalence of approximately 6 % [26, 27]. Portopulmonary hypertension has been classified into mild (mean pulmonary artery pressure 25–35 mmHg), moderate (35–45 mmHg), or severe (>45 mmHg). There seems to be no increased perioperative risk for liver transplant candidates with mild portopulmonary hypertension, whereas moderate and severe disease is associated with increased mortality. Patients with severe portopulmonary hypertension have been reported to have mortality rates as high as 42 % at 9 months [28–31].

9.1.4 Renal System

Acute kidney injury commonly occurs in patients with chronic liver disease and is present in up to 20 % of patients hospitalized with decompensated cirrhosis [32]. Gastrointestinal bleeding, diarrhoea from infection or lactulose administration, and diuretic medications change circulatory function by causing hypovolaemia and can result in prerenal injury [33, 34].

However, the predominant functional cause of renal failure in patients with hepatic failure is hepatorenal syndrome. As cirrhosis progresses, reduction in systemic vascular resistance activates the renin-angiotensin and sympathetic nervous systems, leading to ascites, oedema, and vasoconstriction of the intrarenal circulation and consequently renal hypoperfusion [35]. The identification of patients with advanced renal disease needing combined liver-kidney transplants is of paramount importance in the preoperative setting, but also the treatment of pre-existing acid-base abnormalities and plasma volume defects, which might worsen advanced renal disease in the perioperative period, is fundamental [36–39].

9.1.5 Gastrointestinal System

Portal hypertension from cirrhosis causes oesophageal varices and portal gastropathy. Oesophageal varices are found in about 50 % of patients with cirrhosis at the time of diagnosis [40]. Portal hypertension leads to ascites, which is usually managed medically by dietary sodium restriction and diuretic use [40].

9.1.6 Haematologic and Coagulation System

In patients with hepatic disease, the alterations in the haemostatic capacity of the blood can go towards both bleeding and thrombosis. Inadequate synthesis of all coagulation factors (except for von Willebrand's factor and factor VIII), thrombocytopenia, platelet function defects, dysfibrinogenaemia, and elevated tissue plasminogen activator (tPA) levels can cause bleeding. Elevation of von Willebrand's factor and factor VIII and decreased levels of protein C, protein S, antithrombin, α 2-macroglobulin, plasminogen, and heparin cofactor II can promote thrombosis. Factors VII, X, V, II (prothrombin), and I (fibrinogen) have a short half-life (hours to days) and are synthesized solely

by hepatocytes, making possible a 'semi real-time' evaluation of hepatic synthetic function [41–43]. Levels of fibrinogen, an acute phase reactant, are normal or increased in mild-to-moderate liver disease. In patients with severe hepatic dysfunction, however, fibrinogen is poorly synthesized and dysfunctional, which increases the risk of bleeding [44–49]. Thrombocytopenia results from several factors: portal hypertension with hypersplenism and platelets sequestration, consumption of platelets during systemic intravascular coagulation and impaired hepatic synthesis of thrombopoietin [50, 51]. Moreover, uraemia from acute kidney injury and intrinsic defects of ADP, arachidonic acid, collagen, and thrombin also prevents platelet aggregation by contributing to a defective signal transduction.

9.1.7 Endocrine System

In liver diseases it is widely known that the carbohydrate and protein metabolism is impaired; hence, glucose intolerance and insulin resistance may occur [52].

In acute fulminant hepatitis, depletion of glycogen stores, decreased gluconeogenesis, and other humoral changes may result in a severe hypoglycaemia.

Table 9.1 synthesizes the main organ dysfunctions related to liver cirrhosis.

9.1.8 Preoperative Assessment

Routine tests of interest for the anaesthesiologist include: complete blood count; urea, creatinine, and electrolytes; liver function studies, including albumin and transaminases; coagulation studies, including PTT and INR; virology studies, including hepatitis A, B, and C, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, HIV, varicella zoster virus; blood group and antibody screening; arterial blood gas, if oxygen saturations are low; electrocardiogram; chest X-ray, posteroanterior and lateral; transthoracic echocardiogram, including estimation of pulmonary artery pressures; and pulmonary function studies in smokers or those with a history of pulmonary disease. Additional investigations are typically undertaken at the discretion of the preoperative assessment physician, although many centres use local protocols or guidelines to guide practice [28, 53–57].

In our institution the pre-anaesthetic evaluation is performed in two stages. In the first stage, all LT candidates are examined by the anaesthesiologist; then they are evaluated by a multidisciplinary team (including haematologists, surgeons, anaesthesiologists, cardiologists, specialty nurses, psychologists, transplant coordinators); the patients are then placed in the waiting list.

The assessment of any neurological deterioration occurring after the initial first-stage evaluation is imperative; also signs of progressive metabolic acidosis, infection or sepsis, cardiovascular instability, pulmonary infection, and severe coagulopathy need to be corrected and treated.

The second-stage evaluation is performed immediately before surgery, for the anaesthetic planning. Patients older than 50, with clinical or family history of heart

Table 9.1 Organ response to hepatic dysfunction

Hepatic	Renal electrolyte glucose	Cardiovascular	Pulmonary	Neurologic	Haematologic
Decreased metabolic function	Acute kidney injury	Vasodilated state	Aspiration risk	Hepatic encephalopathy	Bleeding and thrombosis
Decreased gluconeogenesis	Hepatorenal syndrome	Hyperdynamic cardiac function	Hepatopulmonary syndrome	Cerebral oedema	Unreliable INR
Decreased lactate clearance	Hyponatraemia	Cirrhotic cardiomyopathy	Compression atelectasis	Intracranial hypertension	Decreased factor synthesis
Hyperbilirubinaemia	Hypoglycaemia	Drug-induced hypertension	Pleural effusions/ hepatic hydrothorax		Thrombocytopaenia and platelet dysfunction
Varices	Insulin resistance	Portopulmonary hypertension	Acute respiratory distress syndrome		Dysfibrinogenaemia
Portal hypertension					
Ascites					

disease or diabetes, undergo evaluation for CAD with emission computed tomography using technetium-99. In case of CAD the patients undergo arteriography of the coronaries, or, if the examination is considered dangerous, a computed tomography angiography may be preferred. When needed, the patients undergo percutaneous treatment with angioplasty or stenting of the coronary lesions to prepare them for transplant. In case of elevated pulmonary pressures, the patients undergo right-heart catheterization.

9.2 Intraoperative Monitoring and Management of Liver Transplant Recipients

9.2.1 Monitoring

Routine monitoring includes ECG, oxygen saturation, and invasive blood pressure before induction of anaesthesia. Invasive arterial blood pressure monitoring is essential for providing continuous monitoring and evaluate frequent haemodynamic changes. Pulmonary artery catheters, oesophageal Doppler, pulse contour analysis (PiCCO), lithium dilution technique (LIDCO) and transoesophageal echocardiography (TEE) are all used in different centres. TEE has been used only sporadically as a cardiovascular monitor during orthotopic liver transplant. This is most likely because of concerns regarding the risk of provoking haemorrhage of the gastric or oesophageal mucosa in patients with portal hypertension and impaired coagulation [58]. Despite these concerns, in some centres, the use of this technique is routinely used to improve the monitoring of volume status and myocardial function and to assess the response to cardioactive drugs [59]. Intraoperative TEE may provide additional critical information, such as identification of intracardiac thrombi [60] or complications related to TIPSS [61]. Recently, a report presented a case of postreperfusion graft congestion; TEE revealed a haemodynamically significant thrombotic stenosis of the IVC [62]. The PiCCO technology to assess cardiac output is another less invasive monitoring technique compared to pulmonary arterial catheterization. This device enables the assessment of intravascular blood volume and therefore guides a correct intraoperative fluid management [63]. Coagulation monitoring is best provided by thromboelastography (TEG) although platelet count, activated prothrombin time, thromboplastin time, fibrinogen, and fibrinogen decay products can also supply information and guide reintegration therapy [64, 65].

9.2.2 Anaesthesia Management: Induction and Maintenance

Anaesthesia typically is performed in a rapid sequence, and ventilation is started immediately. A steep drop in SpO_2 can occur rapidly after anaesthesia induction in patients with pre-existing hypoxemia and ascites [66].

Generally the patients are ventilated with anaesthesia-integrated machine, with minimal flow technique; a balanced technique is used for maintenance of anaesthesia, with a volatile agent, narcotic and non-depolarizing muscle relaxant [13]. The lungs are ventilated using a protective strategy with a combination of low tidal volumes (6–8 mL/kg), a positive end expiratory pressure of 6–8 cm H_2O and regular recruitment manoeuvres [67, 68]. The effects of the anaesthetic technique on patient outcome are unknown. It has been suggested that isoflurane offers advantages over sevoflurane and desflurane in terms of its impact on splanchnic blood flow; however, the evidence supporting this assertion is weak. Investigations addressing the effects of desflurane had conflicting results. In an animal study, desflurane has been shown to decrease hepatic blood flow in a dose-dependent manner at concentrations up to 1 MAC. However, a human study, although excluding patients with hepatic diseases and achieving non-statistically significant results, has shown increased hepatic blood flow using desflurane compared to isoflurane [69]. Another study comparing the effects of desflurane and sevoflurane in terms of hepatic blood flow and hepatocellular integrity showed that both agents preserved well the hepatic functions, but decreased splanchnic perfusion and oxygen delivery to the liver. The increased metabolism of sevoflurane which is a hundred times that of desflurane is not known to have detrimental effects on the liver [70]. Paralysis is titrated to achieve suppression of the neuromuscular function, assessed using a peripheral nerve stimulator. Cisatracurium may be the preferred neuromuscular blocking agent in patients undergoing liver transplantation because of its organ-independent elimination and diminished histamine release [71, 72].

9.2.3 Intraoperative Management: Preanhepatic Stage

The preanhepatic phase begins with the surgical incision and ends with the cross-clamping of the portal vein, the suprahepatic inferior vena cava, the infrahepatic inferior vena cava, and the hepatic artery. This phase involves dissection and mobilization of the liver and identification of the porta hepatis.

With abdominal incision and drainage of ascites, hypovolaemia typically occurs. During this phase of surgery, ascites is drained, adhesions are taken down, the vascular and biliary structures are identified, and the diseased liver is mobilized. Blood loss during this phase of surgery may be significant. Previous abdominal surgery (including hepatic resection or liver transplant) or previous intra-abdominal sepsis, including spontaneous bacterial peritonitis, may make this phase of surgery more difficult and the bleeding more significant. Coagulation status should always be monitored by inspection of the surgical field. Patients with active sites of bleeding should be transfused with fresh-frozen plasma, packed red blood cells, prothrombin complex concentrates, antifibrinolytic, recombinant factor VIIa (rFVIIa) or platelets [73, 74]. In addition, desmopressin can be considered for patients with concomitant renal dysfunction and uraemic bleeding. Measurements from thromboelastography (TEG) or rotational thromboelastometry (ROTEM) assess the viscoelastic properties of a whole blood sample as a function of time to reflect the

function and interaction of coagulation factors, blood cells and platelets. These measurements detect a hypercoagulable state and distinguish hyperfibrinolysis from other causes of coagulopathy, such as factor depletion or thrombocytopaenia, to offer a composite picture of the clotting cascade [74–93]. The maintenance of a low positive CVP during parenchymal transection is desirable to reduce hepatic venous bleeding and to allow an easier control of venous injury, because a low CVP can be translated into a low pressure in the hepatic veins and sinusoids. However, the risks of a low CVP include cardiovascular instability, air embolism [91, 94, 95] and adverse outcomes including acute renal failure. Thus, maintenance of low venous pressures must be balanced against adequate perfusion of the organs. The use of terlipressin to achieve these goals has been investigated, demonstrating a reduced portal venous pressure whilst maintaining the renal perfusion [96]. However, further studies are required to evaluate its safety in terms of splanchnic perfusion and post-transplantation portal venous blood flow [97].

Hyponatraemia should not be corrected rapidly. A perioperative rise of 21–32 mEq/L in the serum sodium level was associated with central pontine myelinolysis in one report, whereas an increase of 16 mEq/L was not [98]. Citrate intoxication, ionized hypocalcaemia resulting from the infusion of citrate-rich blood products in the absence of hepatic function, is avoided by the administration of calcium chloride. Ionized hypomagnesaemia also results from citrate infusion, but values of ionized magnesium gradually return to normal after graft reperfusion [99].

9.2.4 Intraoperative Management: Anhepatic Stage

The anhepatic stage begins with the occlusion of vascular inflow to the liver and ends with graft reperfusion. There are two major approaches to the removal of the diseased liver: piggyback technique and venovenous bypass [100].

Piggyback technique uses only partial or side clamping of the IVC, with preservation of some caval flow. This technique causes less haemodynamic compromise and leads to shortened operative and warm ischaemia times, reduced red blood cell and blood product use, and similar graft function and survival outcomes [101]. Venovenous bypass (an extracorporeal circuit to bypass the IVC cross-clamp and return venous blood from the portal and lower body districts) [102] attenuates the decrease in preload, improves renal perfusion pressure, lessens splanchnic congestion and delays the development of metabolic acidosis [103]. The use of VVB is not without risk; in fact, air embolism, thromboembolism and incidental decannulation may be fatal or result in significant morbidity. VVB is not uniformly used at all centres [104–106]; a reasonable approach is to consider the use of venovenous bypass only if trial clamping of the IVC causes profound hypotension associated with a dramatically reduced cardiac index, which does not respond to inotropes and volume loading, or if anatomy or surgical expertise

precludes the piggyback approach. A flow rate of 2–3 L/min is targeted, and depending on pre-existing coagulopathy, a small dose of heparin may be given to reduce the risk of in-circuit clot formation. With the exclusion of the native liver from the patient's circulation, there are profound effects on the patient's metabolic state. The most significant change during the anhepatic phase is the loss of the lactate-metabolizing capacity of the liver and a rise in plasma lactate and decrease in plasma pH [107]. This lactic acidosis is exacerbated when the graft liver is reperfused, and thus, many practitioners choose to treat the acidosis during the anhepatic phase to reduce the risk of severe acidosis with reperfusion [107]. In patients with profound preoperative liver failure or if the anhepatic phase is prolonged, it is appropriate to monitor and treat plasma glucose. If large volumes of blood products are transfused during the anhepatic phase, the reduced capacity of the body to metabolize citrate in the absence of the liver can lead to citrate-associated hypocalcaemia. Particular care should therefore be paid to plasma ionized calcium levels during the anhepatic phase to avoid the risk of reduced vascular tone and compromised myocardial contractility [47].

9.2.5 Intraoperative Management: Neohepatic Stage

This phase of the procedure commences with the reperfusion of the liver graft (usually after completion of the vena cava and portal vein anastomoses) and ends with the closure of the skin and transfer of the patient to the recovery area or ICU. During this phase of surgery, the liver graft is reperfused with the recipient's blood via the portal vein, the hepatic artery and the hepatic veins. During this phase, the biliary anastomosis is made. If the recipient's biliary system has unfavourable anatomy or is diseased, the graft biliary system may require anastomosis to the recipient small bowel, significantly prolonging the operating time. During the reperfusion phase, it is vital that the anaesthesiologist responds actively to the physiological changes this phase entails, in order to optimize the conditions for the survival of the graft. Maintenance of appropriate perfusion pressures to the graft and avoidance of high central venous pressures which may contribute to venous congestion are key factors to this purpose. The surgeon is often able to advise the anaesthesiologist about the venous congestion of the graft and its colour and may request lowering the central venous pressure to optimize this situation. In addition, the reperfusion of the graft, which has been previously kept in ice for preservation, represents an important thermal load for the recipient to absorb. It is expected that the recipient's core temperature (measured, e.g., by a temperature probe on the pulmonary artery catheter) will drop approximately 0.5–1 °C in the minutes following reperfusion. A relatively rapid increase in the core temperature of the recipient following this initial dip can be regarded as an important sign of exothermic cellular metabolism and function of the graft. Additionally, improvement in acid-base status and stable glucose levels are

reassuring signs of graft function. Postreperfusion syndrome is the most significant anaesthetic concern during the reperfusion phase. This syndrome consists of severe cardiovascular dysfunction with decreased cardiac output, severe systemic hypotension, bradyarrhythmia, asystole, raised pulmonary artery pressure, and raised pulmonary capillary wedge pressure and central venous pressure [108]. Reperfusion syndrome is usually observed in the first minutes following the reperfusion of the liver graft and, if not managed actively, can cause cardiac arrest. The formal definition of the syndrome has been refined to include a mean arterial pressure drop of at least 30 % for a period of at least 1 min, within 5 min of reperfusion. Postreperfusion syndrome has proven difficult to predict, with only increased age of the liver graft donor being a strong predictive factor. Its occurrence has been associated with poor outcomes in terms of survival and postoperative renal function [109]. It is not clear if these associations are causative. Various methods are used counteract the negative haemodynamic effects of this syndrome with variable effects. These include flushing the graft with cold saline or autologous blood, sequential or partial unclamping of hepatic graft outflow and anticipatory use of various antihistamine agents, vasopressors, calcium, bicarbonate and methylene blue in cases resistant to other treatments [110]. Haemodynamic perturbations are treated with vasopressor agents, including cautious bolus doses of phenylephrine and epinephrine [111]. Calcium chloride and sodium bicarbonate are also often administered, guided by arterial blood gas results. Life-threatening hyperkalaemia requires prompt treatment; calcium chloride and sodium bicarbonate are the drugs of choice. Dialysis should be considered early in the procedure for oliguric patients with elevated potassium levels [109].

9.2.6 Management of Intraoperative Coagulopathy

Patients with active sites of bleeding should be transfused with fresh-frozen plasma (FFP), packed red blood cells, prothrombin complex concentrates, antifibrinolytic agents, recombinant factor VIIa (rFVIIa) or platelets.

Prothrombin complex concentrates (PCCs) contain the vitamin K-dependent clotting factors II, VII, IX and X and the coagulation inhibitors protein C and S, which allow the correction of coagulation alterations using small fluid volumes. Current evidence suggests that even in high-risk patients, PCCs are safe and that thromboembolic events are rare [82, 83].

FFP is often transfused in order to correct a deranged INR; however, the exponential relationship between coagulation factors and the measured value of PT/INR is not always appreciated. It has been shown that FFP is unable to contribute a sufficient amount of coagulation factors to correct PT/INR by 50 % in most cases, even for mildly prolonged PT/INR [84, 85].

Antifibrinolytic therapy reduces blood loss and transfusion requirements [86]; these drugs are recommended for the treatment of fibrinolysis evidenced by microvascular

oozing or TEG/ROTEM clot lysis measurement (CLI < 15). Meta-analyses have shown that both tranexamic acid and aprotinin can reduce RBC transfusion requirements during OLT [87]. Various dosing regimens have been suggested, and it is unknown which is the lowest effective dose. Currently, tranexamic acid is usually given in 1–2 g increments. In the early years of OLT, the routine use of prophylactic antifibrinolytic agents was common, since the mortality associated with massive blood loss was high, and the risk associated with antifibrinolytic drugs was small in comparison. Now that massive haemorrhage is less frequent, antifibrinolytics are no longer recommended for routine prophylaxis [88]. The response to antifibrinolytic agents should be monitored using TEG/ROTEM to guide the administration of further doses.

Hypofibrinogenaemia has also been shown to influence blood product requirements. A baseline MA (maximum amplitude of the clot measured with TEG) of <35 mm at the beginning of the transplant and measured fibrin degradation products >48 mg/L has been demonstrated to lead to hyperfibrinolysis in 100 % of patients [89]. When haemodilution and massive bleeding occur, fibrinogen is the first factor to reach critical levels [90]. A concentration of <1.5–2 g/L increases haemorrhagic tendency, so this value or signs of functional fibrinogen deficit on TEG or ROTEM should trigger immediate fibrinogen repletion [74].

Recombinant factor VII improves haemostasis by directly activating factor X, precipitating the conversion of prothrombin to thrombin to form a haemostatic clot. Factor VII binds to the surface of activated platelets at sites of vascular injury, increasing localized thrombin generation. Several meta-analysis and systematic reviews of the use of factor VII in hepatic surgery (including transplantation) failed to show a reduction in transfusion requirements, but they showed a significant increase in the incidence of arterial thrombotic events [91, 92]. The ESA guidelines for massive bleeding in visceral and transplant surgery echo this with recommendation against the prophylactic use of rFVIIa, reserving its use only as rescue therapy for uncontrolled bleeding.

Intraoperative platelet transfusions have been identified as a strong independent risk factor for survival after OLT, with a greater hazard ratio than RBCs transfused, particularly for TRALI [112]. A low platelet count combined with a low fibrinogen always leads to a reduced MA/MCF and is strongly associated with an increased tendency towards bleeding [93].

A marked heparin-like effect on the TEG at the time of reperfusion is common and is due to both exogenous heparins administered to the organ donor and the release of endogenous heparinoids from the vascular endothelium and activated macrophages, triggered by the ischaemia-reperfusion injury. This does not appear to contribute significantly to the risk of bleeding and is usually a temporary phenomenon, unless graft function is poor [113]. Reversal with protamine is rarely indicated. Native TEG is extremely sensitive to heparin, and endogenous heparin can be detected in some patients even prior to reperfusion [114, 115].

Table 9.2 synthesizes the main intraoperative tips for anaesthesiologic management for every phase of the intervention.

Table 9.2 Main intraoperative tips for anaesthesiologic management for every phase of the intervention

Anaesthetic induction and maintenance	Preanhepatic stage	Anhepatic stage	Neohepatic stage
Routine monitoring electrocardiography pulse oximetry, capnography, temperature, invasive arterial blood pressure, baseline arterial blood gas and thromboelastogram 8.0 F or larger cannulas into peripheral vein	Maintain Hgb >10 g/dl Lower CVP (5 cmH_2O), restriction of fluid administration Infusion of albumin 20 % if severe hypoalbuminaemia or drainage of ascites Epinephrine or dopamine to preserve cardiac output CO >5 L/min	Maintain Hgb >8 g/dl IV fluids to keep CVP around 5 cmH_2O If venovenous bypass maintain flow rate of 1.5/2 L/min	Maintain Hgb >8 g/dl Euvolaemia (CVP 5–10 mmHg) IV adrenaline 10/20 mcg bolus to keep MAP >60 mmHg
Induction of anaesthesia in a rapid sequence, if risk of aspiration Sellick's manoeuvre Fentanyl 1–2 μg/kg, propofol 0.5–2 mg/kg, cisatracurium 0.5–1.0 mg/kg Maintain anaesthesia balanced with minimal flow, low tidal volume (6–8 ml/Kg), positive end expiratory pressure 5–8 cm H_2O if necessary recruitment manoeuvres Venous access 8.0 French bilumen into left internal jugular vein ultrasound-guided or right if use venovenous bypass	Maintain coagulation status by thromboelastography if prolonged R time Prothrombin complex concentrates (if necessary restriction of FFP administration) or FFP If decreased alpha angle reduced MA platelets infusion or fibrinogen concentrates (maintain fibrinogen >2 g/L)	Maintain coagulation status by thromboelastography if increased lysis (CLI <15) Antifibrinolytic therapy	Maintain coagulation status by thromboelastography delayed graft function and heparin-like effect Maintain MA >45 mm with platelet infusion

Invasive monitoring 8.0 French pulmonary catheter into right internal jugular vein transoesophageal echocardiography if portopulmonary hypertension or bypass	Norepinephrine to keep mean blood pressure >60 mmHg	Adrenaline/norepinephrine to preserve blood pressure >60 mmHg and CO >5 L/min	Adrenaline/norepinephrine to preserve blood pressure >60 mmHg and CO >5 L/min
Intravenous antibiotics			Transoesophageal echocardiography if necessary recommend in postreperfusion graft congestion
Warmers	Correct metabolic acidosis, hypocalcaemia, hypomagnesaemia and glycaemia	Correct metabolic acidosis, hypocalcaemia, hypomagnesaemia and glycaemia	Correct metabolic acidosis, hypocalcaemia, hypomagnesaemia, glycaemia and hyperkalaemia
Connect to rapid infusion system (flow rates 500–1,500 mL/min)			After skin closure echo Doppler for intrahepatic flow and transfer to intensive care
Incision			

9.3 Postoperative Management of Liver Transplantation

Intensive care management of liver-transplanted patients mainly focuses on rapid haemodynamic stabilization, early weaning from mechanical ventilation, proper fluid administration, kidney function preservation, identification and prompt treatment of poor graft function and appropriate monitoring and correction of coagulopathy.

9.3.1 Postoperative Ventilatory Support and Weaning from Mechanical Ventilation

In some patients respiratory weaning is feasible immediately at the end of the surgical procedure. Other patients are stabilized in the ICU before discontinuing mechanical ventilation, in order to ensure that liver function is satisfactory. A number of studies suggest that early or very early tracheal extubation (immediately in the operating room or within 3 h postoperatively) has been associated with a persistent maintenance of satisfactory gas exchange. The incidence of reintubation was not increased when compared to patients extubated later [116, 117]. Mandell et al. [118] demonstrated that a protocol for early extubation and rapid transfer of liver recipients from the ICU to the surgical ward did not negatively impact on long-term outcome. In the early extubation protocol, 1- and 3-year graft and patient survival were above the national average at the time. More recently, Biancofiore et al. [117] retrospectively studied 168 patients who underwent orthotopic liver transplantation and identified a number of risk factors for delayed extubation (Table 9.3). The best predictor of successful extubation according to their results was a model for end-stage liver disease (MELD) score less than 11. Finally, it is clear that an optimal patient selection strategy is key for successful early extubation, though definite criteria and timing are not yet well defined by the current literature. Furthermore, it is not possible to generalize results from different centres who recommend this

Table 9.3 Risk factors for delayed extubation in LT patients

Severity of liver disease before surgery (Child-Pugh and MELD score)
UNOS status
Age
Duration of graft ischaemia
Duration of surgery
Primary graft dysfunction
Intraoperative blood requirements
Body temperature on ICU admission
Renal dysfunction
Hepatic encephalopathy
Need to inotropes or vasopressor
Inadequate oxygenation

This table has been adapted from Razonable et al.

strategy, due to differences in the preoperative clinical conditions of the patient populations, the surgical skills and the postoperative resources available.

Mechanical ventilation has a number of potentially detrimental side effects in the liver transplant patient. It can worsen venous congestion of the liver graft by increasing the intrathoracic pressure and reducing venous return from the IVC and hepatic veins [119]; moreover, prolonged mechanical ventilation increases the risk of ventilator-associated pneumonia [120]. Failure of an early extubation strategy may be associated with impaired oxygen delivery to the newly grafted liver.

A difficult weaning from mechanical ventilation is very often a consequence of postoperative respiratory complications. These can be attributed to massive transfusions, pleural effusion, inadequate clearance of bronchial secretions, pneumonia and adverse effects of the immunosuppressive therapy. Acute respiratory distress syndrome (ARDS) is one of the major complications following OLT. Its main causes include a severe reperfusion syndrome, substantial blood loss, prolonged surgical times and early postoperative infections, mainly caused by translocation of gram negative bacteria form the intestinal mucosa. The pathophysiological mechanism of transfusion-related acute lung injury (TRALI), a causative factor of ARDS, seems to be related to donor alloantibodies that react against granulocytes or leucocyte antigens (anti-HLA) [121]. The management and treatment of respiratory complications, including ARDS, are primarily supportive, with obligatory mechanical assistance in cases of ventilatory failure. It is known that ventilation at high intrathoracic pressure may cause venous congestion of the graft increasing the risk of ischaemic damage. The available literature regarding the ventilatory strategy in transplanted liver patients with ARDS provides little evidence, but we have to underline that the preservation of the graft function is mandatory. This can be achieved by privileging the maintenance of a very good oxygenation, even if elevated intrathoracic pressures have to be applied. Sometimes liver transplant patients prove difficult to wean form mechanical ventilation, due to unsatisfactory gas exchange during various T-piece trials. In these circumstances a rapid extubation followed by an immediate application of a noninvasive ventilator support should be considered. Noninvasive ventilation (NIV) by adding a pressure support (PS) with a continuous positive end expiratory pressure (PEEP) could prevent the loss of vital capacity and impede severe lung derecruitment following extubation. As opposed to the first applications in solid organ transplantation, when NIV was mainly delivered by full facial mask [122], nowadays it is predominantly delivered by the helmet system. Daily experience shows that the helmet is more suitable for longer application of NIV. The first application of NIV in solid organ transplant recipients was described by Antonelli et al. [123]. If postoperative respiratory failure is severe enough to require a prolonging of mechanical ventilation, ventilator strategies that minimize insults to both the lung and the allograft should be used. Airway pressures and PEEP should be set in order to improve oxygenation without simultaneously impairing liver outflow. In liver recipients affected by severe ARDS, low tidal volume (6 $mLKg^{-1}$ of ideal body weight), relatively high respiratory rates and PEEP confer a survival advantage by keeping the lung open and avoiding atelectasis and shear stresses on lung units [124]. Mechanical ventilation with high PEEP, as

previously stated, has been reported to impair liver outflow. Besides determining an increase retrograde blood accumulation and liver oedema, an excessive PEEP (>10 cmH_2O) may also depress the splanchnic perfusion and hepatic performance, by increasing venous stasis in the portocaval system and depressing cardiac output. When critical hypoxaemia occurs in the setting of a severe respiratory failure, inhaled nitric oxide may be administered.

9.3.2 Postoperative Haemodynamic Monitoring and Circulatory Stabilization

Because of potential cardiocirculatory instability and the need to optimize cardiac output and organ perfusion, haemodynamic monitoring must be strict in the immediate postoperative period. Maintenance of postoperative graft function depends primarily on liver cell recovery, which can be enhanced by optimizing the liver haemodynamics and preventing venous stasis. Knowledge of the preload and afterload indexes of both right (RV) and left ventricle (LV), mean and transpulmonary pressure and pulmonary vascular resistance (PVR) is useful in managing pharmacologic interventions, volume therapy and vasoactive drug administration. It is useful to insert also a pulmonary artery catheter (PAC) equipped with a fast response thermistor capable of assessing RV ejection fraction (RVEF%) and ventricular filling through RV end-diastolic volume calculation (RVEDV).

Subclinical hypovolaemia or excessive cardiac filling resulting in pulmonary oedema and deterioration of gas exchange may lead to inadequate graft perfusion and increase postoperative morbidity. Patients with cirrhosis tend to have impaired ventricular contractility in response to physiologic stress or pharmacologic stimulation. Additionally, metabolic disturbances, in the form of acidosis, hypothermia and electrolyte disturbances, can further reduce the cardiac performance and lead to circulatory instability. Haemodynamic depression may also be a long-term result of the reperfusion syndrome and/or a consequence of graft nonfunction. Other causes of postoperative hypotension are a pre-existing dilated cardiomyopathy, the potential for coronary artery disease and unrecognized hypovolaemia from various factors, including third space losses, haemorrhage and ongoing ascites formation. The possibility of perioperative myocardial infarction causing left ventricular dysfunction must be kept in mind in cases of refractory circulatory dysfunction. Postoperative ‘subclinical’ pulmonary oedema is not infrequent, with at least 50 % of these episodes developing within the first 24 h. The rapid improvement of systemic vasodilatation with the return of liver graft function, which can result in a sudden increase in the afterload, is another potential cause of excessive strain on the heart. It is known that the evolution of some cardiocirculatory parameter and ossiforetics (progressive increasing in arteriovenous oxygen content) plays an important role as prognostic indexes.

Haemodynamic optimization following orthotopic liver transplant aims at preventing inadequate cardiac filling, which results in suboptimal tissue perfusion and

possible organ failure. Continuous monitoring of dynamic parameters of fluid responsiveness and/or assessment of RV (right ventricular) end-diastolic filling and RV ejection fraction % is helpful in maintaining an adequate central blood volume. Optimizing cardiac output will avoid excessive fluid administration, thus preventing both pulmonary congestion and an unrecognized increase in the sinusoidal and hepatic vein pressures. In liver-transplanted patients, a vasodilated and hyperdynamic state may take days or weeks to regress to near-normal levels. Moderate filling followed by vasoconstriction should effectively treat this evolving clinical condition. Infusion of norepinephrine is usually started in the operating room to ameliorate the hyperkinetic status of the patients and continued in ICU to achieve a good mean arterial pressure and thus a good perfusion of the new liver.

A correct fluid and electrolyte balance in the immediate recovery period in the ICU is also mandatory. Many studies demonstrate that one of the significant predictors of readmission to the ICU of the transplanted patients was the amount of blood product administered intraoperatively [125]. Generous fluid replacement may result in volume overload, water-sodium retention and capillary leak syndrome in the third space and may further worsen graft congestion and oedema caused by ischaemia-reperfusion syndrome. Once the postoperative haemodynamics have been stabilized, it is necessary to promote the return of the sequestered fluid from the peripheral circulation and third space, back to the central circulation. An appropriate negative fluid balance in the first days after operation apparently decreases the incidence of early pulmonary complications and may be associated with improved oxygen delivery to the graft. Lowering right ventricular volume and pressure would create a venous pressure gradient between the portal and the central venous circulation that draws blood through the donor graft. A rationale approach to maintaining circulating volume is by providing two-thirds of required fluids with crystalloids and replacing half of drain loss with 5 % albumin solution. The real advantage of albumin solutions on the final outcome is still under debate as the evidence for a specific benefit as been substantial only in the settings of decompensated cirrhosis. A few reports have addressed the use of albumin after orthotopic liver transplant [126]. Although the postoperative transfusion policies may differ among centres, the replacement of blood components to achieve haemoglobin between 8 and 10 g L^{-1}, as commonly adopted during transplant surgery, could be a valid approach [127]. Maintaining a postoperative haematocrit between 25 and 30 % would be helpful to guarantee an adequate oxygen delivery to the new graft. Disturbances of the metabolic function of different organs and alterations of the hormonal balance are very common and mainly caused by ischaemia-reperfusion injury, surgical stress and pre-existing pathologies and the various drugs administered to the patients. Common disturbances include alteration of metabolism of glucose, of lactate levels and of electrolytes. Hyperglycaemia is the most frequent alteration, and it is due to the preoperative stress, liberation of endogenous catecolamines, administration of high-dose steroids to induce immunosuppression, chronic immunosuppressive therapy (calcineurin inhibitors) and glucose given for enteral or parenteral nutrition. A tight control of blood glucose levels is mandatory and best achieved by continuous infusion of insulin. Hyperglycaemia is very common and usually lasts until a good

peripheral utilization of glucose and normalization of the endogenous hormonal secretion returns. This is greatly ameliorated by an early enteral feeding. The persistence of hypoglycaemia on the other hand can be a picket sign of a compromised liver recovery.

9.3.3 AKI and Renal Failure

The occurrence of AKI [128] in patients undergoing liver transplant is associated with reduced patient and graft survival not only in the perioperative period but also in the longer term [129, 130] with reports of 10 % of patients progressing to end-stage renal failure. AKI reduces patient survival and leads to increased health care and hospital stay. Furthermore, increasing evidence supports the fact that even relatively minor deteriorations in renal function not requiring renal replacement therapy are associated with inferior patient and renal outcomes in the longer term: this underlines the importance of the early identification of 'at-risk individuals' and the need to identify preventative strategies. AKI post liver transplant is not an infrequent problem and has been reported to occur in 9–78 % of cases [131, 132]. This marked variability in the reported incident rates can be predominantly attributed to the different underlying aetiologies and definitions of AKI used. Definitions of AKI have varied and only recently has a consensus definition based on the risk, injury, failure, loss and end-stage kidney disease (RIFLE) criteria been introduced [133]. This staging system has been modified by the Acute Kidney Injury Network (AKIN) to define AKI as a rise in serum creatinine levels within a 48-h frame and also stresses the importance of a relatively small rise in serum creatinine levels.

When AKI is defined as at least a doubling of serum creatinine levels or the need for dialysis (RIFLE grade 1 or F or AKIN stages 2 or 3), the incidence of AKI is approximately 9–48 % [132, 134]. Clearly, the aetiology of AKI post liver transplant can be multifactorial because these patients are frequently critically ill in the perioperative period. Renal insult can occur during septic episodes or periods of haemodynamic instability and hypovolaemia due to intraoperative blood loss, and this can result in prerenal failure or ischaemic injury. Immediately after the operation, the risk of developing AKI depends primarily on the aforementioned factors, the severity of liver disease, the preoperative renal function and the postoperative liver function. Furthermore, several studies have reported an increased risk of AKI associated with poor graft function or primary non function (PNF) [135] postoperative [131, 136]. Elevated intra-abdominal pressure is well established as a risk factor for AKI; however, there has been no formal evaluation of whether there is a critical threshold of abdominal pressure after liver transplant [137]. Major causes of late postoperative AKI (i.e. after the first 3 days) include bacterial infections, retransplantation and exploratory surgery for delayed haemorrhaging and surgical leaks [138]. However, the single most important cause of renal injury remains drug-induced toxicity. Ciclosporin and tacrolimus can lead to renal injury [139]. Acute renal injury due to calcineurin inhibitors has been reported to increase almost threefold the odds ratio for developing chronic kidney disease within 10 years [140].

Independently of the cause of renal injury, starting the renal replacement therapy remains a clinical decision: fluid overload and electrolyte disturbances are the most common trigger factors [141], and they are followed by metabolic acidosis rather than urea and creatinine levels per se [142]. The choice of the renal replacement modality should be guided by each patient's clinical status, the medical and nursing expertise and the available modalities.

References

1. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60:715–35. doi:10.1002/hep.27210.
2. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy–definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology. 2002;35:716–21. doi:10.1053/jhep.2002.31250.
3. Córdoba J. New assessment of hepatic encephalopathy. J Hepatol. 2011;54:1030–40. doi:10.1016/j.jhep.2010.11.015.
4. Lockwood AH. Blood ammonia levels and hepatic encephalopathy. Metab Brain Dis. 2004;19:345–9.
5. Chavarria L, Alonso J, García-Martínez R, Simón-Talero M, Ventura-Cots M, Ramírez C, et al. Brain magnetic resonance spectroscopy in episodic hepatic encephalopathy. J Cereb Blood Flow Metab. 2013;33:272–7. doi:10.1038/jcbfm.2012.173.
6. Grønbaek H, Johnsen SP, Jepsen P, Gislum M, Vilstrup H, Tage-Jensen U, et al. Liver cirrhosis, other liver diseases, and risk of hospitalisation for intracerebral haemorrhage: a Danish population-based case-control study. BMC Gastroenterol. 2008;8:16. doi:10.1186/1471-230X-8-16.
7. Martin P, DiMartini A, Feng S, Brown R, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Hepatology. 2014;59:1144–65.
8. Lucey MR, Terrault N, Ojo L, Hay JE, Neuberger J, Blumberg E, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl. 2013;19:3–26. doi:10.1002/lt.23566.
9. Herrero JI, Bilbao JI, Diaz ML, Alegre F, Inarrairaegui M, Pardo F, et al. Hepatic encephalopathy after liver transplantation in a patient with a normally functioning graft: treatment with embolization of portosystemic collaterals. Liver Transpl. 2009;15:111–4. doi:10.1002/lt.21552.
10. Iwakiri Y, Groszmann RJ. The hyperdynamic circulation of chronic liver diseases: from the patient to the molecule. Hepatology. 2006;43:S121–31. doi:10.1002/hep.20993.
11. Hennenberg M, Trebicka J, Sauerbruch T, Heller J. Mechanisms of extrahepatic vasodilation in portal hypertension. Gut. 2008;57:1300–14. doi:10.1136/gut.2007.144584.
12. Vaughan RB, Angus PW, Chin-Dusting JPF. Evidence for altered vascular responses to exogenous endothelin-1 in patients with advanced cirrhosis with restoration of the normal vasoconstrictor response following successful liver transplantation. Gut. 2003;52:1505–10.
13. Hall TH, Dhir A. Anesthesia for liver transplantation. Semin Cardiothorac Vasc Anesth. 2013;17:180–94. doi:10.1177/1089253213481115.
14. Møller S, Bendtsen F, Henriksen JH. Pathophysiological basis of pharmacotherapy in the hepatorenal syndrome. Scand J Gastroenterol. 2005;40:491–500. doi:10.1080/00365520510012064.
15. Biancofiore G, Mandell MS, Rocca G, Della. Perioperative considerations in patients with cirrhotic cardiomyopathy. Curr Opin Anaesthesiol. 2010;23:128–32. doi:10.1097/ACO.0b013e328337260a.

16. Møller S, Hove JD, Dixen U, Bendtsen F. New insights into cirrhotic cardiomyopathy. Int J Cardiol. 2013;167:1101–8. doi:10.1016/j.ijcard.2012.09.089.
17. Plotkin JS, Scott VL, Pinna A, Dobsch BP, De Wolf AM, Kang Y. Morbidity and mortality in patients with coronary artery disease undergoing orthotopic liver transplantation. Liver Transpl Surg. 1996;2:426–30.
18. Appleton CP, Hurst RT. Reducing coronary artery disease events in liver transplant patients: moving toward identifying the vulnerable patient. Liver Transpl. 2008;14:1691–3. doi:10.1002/lt.21660.
19. Gologorsky E, Pretto EA, Fukazawa K. Coronary artery disease and its risk factors in patients presenting for liver transplantation. J Clin Anesth. 2013;25:618–23. doi:10.1016/j.jclinane.2013.06.001.
20. Yong CM, Sharma M, Ochoa V, Abnousi F, Roberts J, Bass NM, et al. Multivessel coronary artery disease predicts mortality, length of stay, and pressor requirements after liver transplantation. Liver Transpl. 2010;16:1242–8. doi:10.1002/lt.22152.
21. Tiukinhoy-Laing SD, Rossi JS, Bayram M, De Luca L, Gafoor S, Blei A, et al. Cardiac hemodynamic and coronary angiographic characteristics of patients being evaluated for liver transplantation. Am J Cardiol. 2006;98:178–81. doi:10.1016/j.amjcard.2006.01.089.
22. Rodríquez-Roisin R, Krowka MJ, Hervé P, Fallon MB. Highlights of the ERS task force on pulmonary-hepatic vascular disorders (PHD). J Hepatol. 2005;42:924–7.
23. Machicao VI, Fallon MB. Hepatopulmonary syndrome. Semin Respir Crit Care Med. 2012;33:11–6. doi:10.1055/s-0032-1301730.
24. Hemprich U, Papadakos PJ, Lachmann B. Respiratory failure and hypoxemia in the cirrhotic patient including hepatopulmonary syndrome. Curr Opin Anaesthesiol. 2010;23:133–8. doi:10.1097/ACO.0b013e328335f024.
25. Rodríguez-Roisin R, Krowka MJ, Hervé P, Fallon MB. Pulmonary-hepatic vascular disorders (PHD). Eur Respir J. 2004;24:861–80. doi:10.1183/09031936.04.00010904.
26. Colle IO, Moreau R, Godinho E, Belghiti J, Ettori F, Cohen-Solal A, et al. Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study. Hepatology. 2003;37:401–9. doi:10.1053/jhep.2003.50060.
27. Krowka MJ, Swanson KL, Frantz RP, McGoon MD, Wiesner RH. Portopulmonary hypertension: results from a 10-year screening algorithm. Hepatology. 2006;44:1502–10. doi:10.1002/hep.21431.
28. Murray KF, Carithers RL. AASLD practice guidelines: evaluation of the patient for liver transplantation. Hepatology. 2005;41:1407–32. doi:10.1002/hep.20704.
29. Machicao VI, Balakrishnan M, Fallon MB. Pulmonary complications in chronic liver disease. Hepatology. 2014;59:1627–37. doi:10.1002/hep.26745.
30. Fritz JS, Fallon MB, Kawut SM. Pulmonary vascular complications of liver disease. Am J Respir Crit Care Med. 2013;187:133–43. doi:10.1164/rccm.201209-1583CI.
31. Krowka MJ, Wiesner RH, Heimbach JK. Pulmonary contraindications, indications and MELD exceptions for liver transplantation: a contemporary view and look forward. J Hepatol. 2013;59:367–74. doi:10.1016/j.jhep.2013.03.026.
32. Hartleb M, Gutkowski K. Kidneys in chronic liver diseases. World J Gastroenterol. 2012;18:3035–49. doi:10.3748/wjg.v18.i24.3035.
33. Meltzer J, Brentjens TE. Renal failure in patients with cirrhosis: hepatorenal syndrome and renal support strategies. Curr Opin Anaesthesiol. 2010;23:139–44. doi:10.1097/ACO.0b013e32833724a8.
34. Ginès P, Schrier RW. Renal failure in cirrhosis. N Engl J Med. 2009;361:1279–90. doi:10.1056/NEJMra0809139.
35. Steadman RH, Van Rensburg A, Kramer DJ. Transplantation for acute liver failure: perioperative management. Curr Opin Organ Transplant. 2010;15:368–73. doi:10.1097/MOT.0b013e32833982dd.
36. Cárdenas A, Uriz J, Ginès P, Arroyo V. Hepatorenal syndrome. Liver Transpl. 2000;6:S63–71.
37. Angeli P, Morando F, Cavallin M, Piano S. Hepatorenal syndrome. Contrib Nephrol. 2011;174:46–55. doi:10.1159/000329235.

38. Uriz J, Ginès P, Cárdenas A, Sort P, Jiménez W, Salmerón JM, et al. Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. J Hepatol. 2000;33:43–8.
39. Solanki P, Chawla A, Garg R, Gupta R, Jain M, Sarin SK. Beneficial effects of terlipressin in hepatorenal syndrome: a prospective, randomized placebo-controlled clinical trial. J Gastroenterol Hepatol. 2003;18:152–6.
40. Rahimi RS, Rockey DC. Complications of cirrhosis. Curr Opin Gastroenterol. 2012;28: 223–9. doi:10.1097/MOG.0b013e328351d003.
41. Takikawa Y, Harada M, Wang T, Suzuki K. Usefulness and accuracy of the international normalized ratio and activity percent of prothrombin time in patients with liver disease. Hepatol Res. 2014;44:92–101. doi:10.1111/hepr.12093.
42. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med. 2011;365:147–56. doi:10.1056/NEJMra1011170.
43. Steib A, Freys G, Lehmann C, Meyer C, Mahoudeau G. Intraoperative blood losses and transfusion requirements during adult liver transplantation remain difficult to predict. Can J Anaesth. 2001;48:1075–9. doi:10.1007/BF03020372.
44. Lisman T, Caldwell SH, Burroughs AK, Northup PG, Senzolo M, Stravitz RT, et al. Hemostasis and thrombosis in patients with liver disease: the ups and downs. J Hepatol. 2010;53:362–71. doi:10.1016/j.jhep.2010.01.042.
45. Martinez J, MacDonald KA, Palascak JE. The role of sialic acid in the dysfibrinogenemia associated with liver disease: distribution of sialic acid on the constituent chains. Blood. 1983;61:1196–202.
46. Caldwell SH, Hoffman M, Lisman T, Macik BG, Northup PG, Reddy KR, et al. Coagulation disorders and hemostasis in liver disease: pathophysiology and critical assessment of current management. Hepatology. 2006;44:1039–46. doi:10.1002/hep.21303.
47. Hannaman MJ, Hevesi ZG. Anesthesia care for liver transplantation. Transplant Rev (Orlando). 2011;25:36–43. doi:10.1016/j.trre.2010.10.004.
48. Colucci M, Binetti BM, Branca MG, Clerici C, Morelli A, Semeraro N, et al. Deficiency of thrombin activatable fibrinolysis inhibitor in cirrhosis is associated with increased plasma fibrinolysis. Hepatology. 2003;38:230–7. doi:10.1053/jhep.2003.50277.
49. Lisman T, Leebeek FW, Mosnier LO, Bouma BN, Meijers JC, Janssen HL, et al. Thrombin-activatable fibrinolysis inhibitor deficiency in cirrhosis is not associated with increased plasma fibrinolysis. Gastroenterology. 2001;121:131–9.
50. Lisman T, Leebeek FWG. Hemostatic alterations in liver disease: a review on pathophysiology, clinical consequences, and treatment. Dig Surg. 2007;24:250–8. doi:10.1159/000103655.
51. Wiklund RA. Preoperative preparation of patients with advanced liver disease. Crit Care Med. 2004;32:S106–15.
52. DeWolf AM, Kang YG, Todo S, Kam I, Francavilla AJ, Polimeno L, et al. Glucose metabolism during liver transplantation in dogs. Anesth Analg. 1987;66:76–80.
53. Ehtisham J, Altieri M, Salamé E, Saloux E, Ollivier I, Hamon M. Coronary artery disease in orthotopic liver transplantation: pretransplant assessment and management. Liver Transpl. 2010;16:550–7. doi:10.1002/lt.22035.
54. Vogt DP, Henderson JM, Carey WD, Barnes D. The long-term survival and causes of death in patients who survive at least 1 year after liver transplantation. Surgery. 2002;132:775–80; discussion 780.
55. Aydinalp A, Bal U, Atar I, Ertan C, Aktaş A, Yildirir A, et al. Value of stress myocardial perfusion scanning in diagnosis of severe coronary artery disease in liver transplantation candidates. Transplant Proc. 2009;41:3757–60. doi:10.1016/j.transproceed.2009.06.219.
56. Rabkin JM, Corless CL, Rosen HR, Olyaei AJ. Immunosuppression impact on long-term cardiovascular complications after liver transplantation. Am J Surg. 2002;183:595–9.
57. Keeling AN, Flaherty JD, Davarpanah AH, Ambrosy A, Farrelly CT, Harinstein ME, et al. Coronary multidetector computed tomographic angiography to evaluate coronary artery disease in liver transplant candidates: methods, feasibility and initial experience. J Cardiovasc Med (Hagerstown). 2011;12:460–8. doi:10.2459/JCM.0b013e3283483916.

58. Burger-Klepp U, Karatosic R, Thum M, Schwarzer R, Fuhrmann V, Hetz H, et al. Transesophageal echocardiography during orthotopic liver transplantation in patients with esophagoastric varices. Transplantation. 2012;94:192–6. doi:10.1097/TP.0b013e31825475c2.
59. López-Candales A, Menendez FL, Shah SA, Friedrich A. Measures of right ventricular systolic function in end stage liver disease patients awaiting transplant. Int J Cardiol. 2014;171:277–8. doi:10.1016/j.ijcard.2013.11.088.
60. Nanashima A, Pillay P, Crawford M, Nakasuji M, Verran DJ, Painter D. Analysis of postrevascularization syndrome after orthotopic liver transplantation: the experience of an Australian liver transplantation center. J Hepatobiliary Pancreat Surg. 2001;8:557–63. doi:10.1007/s005340100025.
61. Perilli V, Avolio AW, Sacco T, Modesti C, Gaspari R, Caserta R, et al. Use of an esophageal echo-Doppler device during liver transplantation: preliminary report. Transpl Proc. 2009;41:198–200. doi:10.1016/j.transproceed.2008.09.054.
62. Schober P, Loer SA, Schwarte LA. Perioperative hemodynamic monitoring with transesophageal Doppler technology. Anesth Analg. 2009;109:340–53. doi:10.1213/ane.0b013e3181aa0af3.
63. Della Rocca G, Costa GM, Coccia C, Pompei L, Di Marco P, Pietropaoli P. Preload index: pulmonary artery occlusion pressure versus intrathoracic blood volume monitoring during lung transplantation. Anesth Analg. 2002;95:835–43, table of contents.
64. Feltracco P, Brezzi M, Barbieri S, Galligioni H, Milevoj M, Carollo C, et al. Blood loss, predictors of bleeding, transfusion practice and strategies of blood cell salvaging during liver transplantation. World J Hepatol. 2013;5:1–15. doi:10.4254/wjh.v5.i1.1.
65. Wang S-C, Lin H-T, Chang K-Y, Mandell MS, Ting C-K, Chu Y-C, et al. Use of higher thromboelastogram transfusion values is not associated with greater blood loss in liver transplant surgery. Liver Transpl. 2012;18:1254–8. doi:10.1002/lt.23494.
66. Kim JA, Lee JJ, Kim CS, Chung IS, Gwak MS, Kim GS. Does general anesthesia with inhalation anesthetics worsen hypoxemia in patients with end-stage liver disease and an intrapulmonary shunt? Transplant Proc. 2011;43:1665–8. doi:10.1016/j.transproceed.2011.03.056.
67. Futier E, Constantin J-M, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med. 2013;369:428–37. doi:10.1056/NEJMoa1301082.
68. Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. Lancet. 2010;376:190–201. doi:10.1016/S0140-6736(10)60274-7.
69. Molin SZFD, Kruel CRP, de Fraga RS, Alboim C, de Oliveira JR, Alvares-da-Silva MR. Differential protective effects of anaesthesia with sevoflurane or isoflurane: an animal experimental model simulating liver transplantation. Eur J Anaesthesiol. 2014. doi:10.1097/EJA.0000000000000127.
70. Steadman RH. Anesthesia for liver transplant surgery. Anesthesiol Clin North America. 2004;22:687–711. doi:10.1016/j.atc.2004.06.009.
71. Marcel RJ, Ramsay MA, Hein HA, Nguyen AT, Ramsay KJ, Suit CT, et al. Duration of rocuronium-induced neuromuscular block during liver transplantation: a predictor of primary allograft function. Anesth Analg. 1997;84:870–4.
72. De Wolf AM, Freeman JA, Scott VL, Tullock W, Smith DA, Kisor DF, et al. Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation. Br J Anaesth. 1996;76:624–8.
73. Clevenger B, Mallett SV. Transfusion and coagulation management in liver transplantation. World J Gastroenterol. 2014;20:6146–58. doi:10.3748/wjg.v20.i20.6146.
74. Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CAA, De Robertis E, Filipescu DC, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol. 2013;30:270–382. doi:10.1097/EJA.0b013e32835f4d5b.
75. Dalmau A, Sabaté A, Aparicio I. Hemostasis and coagulation monitoring and management during liver transplantation. Curr Opin Organ Transplant. 2009;14:286–90. doi:10.1097/MOT.0b013e32832a6b7c.

76. Krzanicki D, Sugavanam A, Mallett S. Intraoperative hypercoagulability during liver transplantation as demonstrated by thromboelastography. Liver Transpl. 2013;19:852–61. doi:10.1002/lt.23668.
77. Mallett SV, Chowdary P, Burroughs AK. Clinical utility of viscoelastic tests of coagulation in patients with liver disease. Liver Int. 2013;33:961–74. doi:10.1111/liv.12158.
78. Tripodi A, Primignani M, Chantarangkul V, Viscardi Y, Dell'Era A, Fabris FM, et al. The coagulopathy of cirrhosis assessed by thromboelastometry and its correlation with conventional coagulation parameters. Thromb Res. 2009;124:132–6. doi:10.1016/j.thromres.2008.11.008.
79. Sihler KC, Napolitano LM. Complications of massive transfusion. Chest. 2010;137:209–20. doi:10.1378/chest. 09-0252.
80. Levy JH, Fingerhut A, Brott T, Langbakke IH, Erhardtsen E, Porte RJ. Recombinant factor VIIa in patients with coagulopathy secondary to anticoagulant therapy, cirrhosis, or severe traumatic injury: review of safety profile. Transfusion. 2006;46:919–33. doi:10.1111/j.1537-2995.2006.00824.x.
81. Shao Y-F, Yang J-M, Chau G-Y, Sirivatanauksorn Y, Zhong S-X, Erhardtsen E, et al. Safety and hemostatic effect of recombinant activated factor VII in cirrhotic patients undergoing partial hepatectomy: a multicenter, randomized, double-blind, placebo-controlled trial. Am J Surg. 2006;191:245–9. doi:10.1016/j.amjsurg.2005.10.019.
82. Franchini M, Lippi G. Prothrombin complex concentrates: an update. Blood Transfus. 2010;8:149–54. doi:10.2450/2010.0149-09.
83. Arshad F, Ickx B, van Beem RT, Polak W, Grüne F, Nevens F, et al. Prothrombin complex concentrate in the reduction of blood loss during orthotopic liver transplantation: PROTON-trial. BMC Surg. 2013;13:22. doi:10.1186/1471-2482-13-22.
84. Abdel-Wahab OI, Healy B, Dzik WH. Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. Transfusion. 2006;46:1279–85. doi:10.1111/j.1537-2995.2006.00891.x.
85. Fries D, Haas T, Klingler A, Streif W, Klima G, Martini J, et al. Efficacy of fibrinogen and prothrombin complex concentrate used to reverse dilutional coagulopathy–a porcine model. Br J Anaesth. 2006;97:460–7. doi:10.1093/bja/ael191.
86. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2011;(1):CD001886. doi:10.1002/14651858.CD001886.pub4.
87. Molenaar IQ, Warnaar N, Groen H, Tenvergert EM, Slooff MJH, Porte RJ. Efficacy and safety of antifibrinolytic drugs in liver transplantation: a systematic review and meta-analysis. Am J Transplant. 2007;7:185–94. doi:10.1111/j.1600-6143.2006.01591.x.
88. Görlinger K. Coagulation management during liver transplantation. Hamostaseologie. 2006;26:S64–76.
89. Steib A, Gengenwin N, Freys G, Boudjema K, Levy S, Otteni JC. Predictive factors of hyperfibrinolytic activity during liver transplantation in cirrhotic patients. Br J Anaesth. 1994;73:645–8.
90. Hiippala ST, Myllylä GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesth Analg. 1995;81:360–5.
91. Chavez-Tapia NC, Alfaro-Lara R, Tellez-Avila F, Barrientos-Gutiérrez T, González-Chon O, Mendez-Sanchez N, et al. Prophylactic activated recombinant factor VII in liver resection and liver transplantation: systematic review and meta-analysis. PLoS One. 2011;6:e22581. doi:10.1371/journal.pone.0022581.
92. Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor VII in randomized clinical trials. N Engl J Med. 2010;363:1791–800. doi:10.1056/NEJMoa1006221.
93. Görlinger K, Dirkmann D, Hanke AA, Kamler M, Kottenberg E, Thielmann M, et al. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. Anesthesiology. 2011;115:1179–91. doi:10.1097/ALN.0b013e31823497dd.

94. Gurusamy KS, Pissanou T, Pikhart H, Vaughan J, Burroughs AK, Davidson BR. Methods to decrease blood loss and transfusion requirements for liver transplantation. Cochrane Database Syst Rev. 2011;(12):CD009052. doi:10.1002/14651858.CD009052.pub2.
95. Massicotte L, Denault AY, Beaulieu D, Thibeault L, Hevesi Z, Nozza A, et al. Transfusion rate for 500 consecutive liver transplantations: experience of one liver transplantation center. Transplantation. 2012;93:1276–81. doi:10.1097/TP.0b013e318250fc25.
96. Mukhtar A, Salah M, Aboulfetouh F, Obayah G, Samy M, Hassanien A, et al. The use of terlipressin during living donor liver transplantation: effects on systemic and splanchnic hemodynamics and renal function. Crit Care Med. 2011;39:1329–34. doi:10.1097/CCM.0b013e3182120842.
97. Delva E, Nordlinger B, Parc R, Lienhart A, Hannoun L, Huguet C. Hepatic vascular exclusion (HVE) for major liver resections. Int Surg. 1987;72:78–81.
98. Wszolek ZK, McComb RD, Pfeiffer RF, Steg RE, Wood RP, Shaw BW, et al. Pontine and extrapontine myelinolysis following liver transplantation. Relationship to serum sodium. Transplantation. 1989;48:1006–12.
99. Scott VL, De Wolf AM, Kang Y, Altura BT, Virji MA, Cook DR, et al. Ionized hypomagnesemia in patients undergoing orthotopic liver transplantation: a complication of citrate intoxication. Liver Transpl Surg. 1996;2:343–7.
100. Levi DM, Pararas N, Tzakis AG, Nishida S, Tryphonopoulos P, Gonzalez-Pinto I, et al. Liver transplantation with preservation of the inferior vena cava: lessons learned through 2,000 cases. J Am Coll Surg. 2012;214:691–8. doi:10.1016/j.jamcollsurg.2011.12.039; discussion 698–9.
101. Vieira de Melo PS, Miranda LEC, Batista LL, Neto OCLF, Amorim AG, Sabat BD, et al. Orthotopic liver transplantation without venovenous bypass using the conventional and piggyback techniques. Transplant Proc. 2011;43:1327–33. doi:10.1016/j.transproceed.2011.03.061.
102. Fonouni H, Mehrabi A, Soleimani M, Müller SA, Büchler MW, Schmidt J. The need for venovenous bypass in liver transplantation. HPB (Oxford). 2008;10:196–203. doi:10.1080/13651820801953031.
103. Rossi G, Langer M, Maggi U, Reggiani P, Caccamo L, Gatti S, et al. Veno-venous bypass versus no bypass in orthotopic liver transplantation: hemodynamic, metabolic, and renal data. Transplant Proc. 1998;30:1871–3.
104. Prager MC, Gregory GA, Ascher NL, Roberts JP. Massive venous air embolism during orthotopic liver transplantation. Anesthesiology. 1990;72:198–200.
105. Calne RY, Rolles K, Farman JV, Kneeshaw JD, Smith DP, Wheeldon DR. Veno-arterial bypass in orthotopic liver grafting. Lancet. 1984;2:1269.
106. Kaufman RD, Khoury GF. Hemodynamic changes with initiation of veno-venous bypass in orthotopic liver transplant patients. Am J Anesthesiol. 1995;22:184–8.
107. Shangraw RE, Winter R, Hromco J, Robinson ST, Gallaher EJ. Amelioration of lactic acidosis with dichloroacetate during liver transplantation in humans. Anesthesiology. 1994;81:1127–38.
108. Ramsay M. The reperfusion syndrome: have we made any progress? Liver Transpl. 2008;14:412–4. doi:10.1002/lt.21418.
109. Paugam-Burtz C, Kavafyan J, Merckx P, Dahmani S, Sommacale D, Ramsay M, et al. Postreperfusion syndrome during liver transplantation for cirrhosis: outcome and predictors. Liver Transpl: Off Publ Am Assoc Study Liver Dis Int Liver Transpl Soc. 2009;15:522–9. doi:10.1002/lt.21730.
110. Cheng SS, Berman GW, Merritt GR, Hendrickse A, Fiegel MJ, Teitelbaum I, et al. The response to methylene blue in patients with severe hypotension during liver transplantation. J Clin Anesth. 2012;24:324–8. doi:10.1016/j.jclinane.2011.10.010.
111. Zhang L, Li M, Yang L. Effects of different vasopressors on hemodynamics in patients undergoing orthotopic liver transplantation. Chin Med J (Engl). 2005;118:1952–8.
112. De Boer MT, Christensen MC, Asmussen M, van der Hilst CS, Hendriks HGD, Slooff MJH, et al. The impact of intraoperative transfusion of platelets and red blood cells on survival after liver transplantation. Anesth Analg. 2008;106:32–44. doi:10.1213/01.ane.0000289638.26666.ed, table of contents.

113. Harding SA, Mallett SV, Peachey TD, Cox DJ. Use of heparinase modified thrombelastography in liver transplantation. Br J Anaesth. 1997;78:175–9.
114. Kettner SC, Gonano C, Seebach F, Sitzwohl C, Acimovic S, Stark J, et al. Endogenous heparin-like substances significantly impair coagulation in patients undergoing orthotopic liver transplantation. Anesth Analg. 1998;86:691–5.
115. Agarwal S, Senzolo M, Melikian C, Burroughs A, Mallett SV. The prevalence of a heparin-like effect shown on the thromboelastograph in patients undergoing liver transplantation. Liver Transpl. 2008;14:855–60. doi:10.1002/lt.21437.
116. Glanemann M, Busch T, Neuhaus P, Kaisers U. Fast tracking in liver transplantation. Immediate postoperative tracheal extubation: feasibility and clinical impact. Swiss Med Wkly. 2007;137:187–91. doi:2007/13/smw-11681.
117. Biancofiore G, Bindi ML, Romanelli AM, Boldrini A, Bisà M, Esposito M, et al. Fast track in liver transplantation: 5 years' experience. Eur J Anaesthesiol. 2005;22:584–90.
118. Mandell MS, Lezotte D, Kam I, Zamudio S. Reduced use of intensive care after liver transplantation: influence of early extubation. Liver Transpl. 2002;8:676–81. doi:10.1053/jlts.2002.34379.
119. Jullien T, Valtier B, Hongnat JM, Dubourg O, Bourdarias JP, Jardin F. Incidence of tricuspid regurgitation and vena caval backward flow in mechanically ventilated patients. A color Doppler and contrast echocardiographic study. Chest. 1995;107:488–93.
120. Chastre J. Conference summary: ventilator-associated pneumonia. Respir Care. 2005;50:975–83.
121. Looney MR, Gropper MA, Matthay MA. Transfusion-related acute lung injury: a review. Chest. 2004;126:249–58. doi:10.1378/chest.126.1.249.
122. Antonelli M, Conti G, Bufi M, Costa MG, Lappa A, Rocco M, et al. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. JAMA. 2000;283:235–41.
123. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000;342:1301–8. doi:10.1056/NEJM200005043421801.
124. Steltzer H, Hiesmayr M, Tüchy G, Zimpfer M. Perioperative liver graft function: the role of oxygen transport and utilization. Anesth Analg. 1993;76:574–9.
125. Mandell MS, Tsou M-Y. The development of perioperative practices for liver transplantation: advances and current trends. J Chin Med Assoc. 2008;71:435–41. doi:10.1016/S1726-4901(08)70145-X.
126. Mukhtar A, EL Masry A, Moniem AA, Metini M, Fayez A, Khater YH. The impact of maintaining normal serum albumin level following living related liver transplantation: does serum albumin level affect the course? A pilot study. Transplant Proc. 2007;39:3214–8. doi:10.1016/j.transproceed.2007.06.084.
127. Ramos E, Dalmau A, Sabate A, Lama C, Llado L, Figueras J, et al. Intraoperative red blood cell transfusion in liver transplantation: influence on patient outcome, prediction of requirements, and measures to reduce them. Liver Transpl. 2003;9:1320–7. doi:10.1016/jlts.2003.50204.
128. Barri YM, Sanchez EQ, Jennings LW, Melton LB, Hays S, Levy MF, et al. Acute kidney injury following liver transplantation: definition and outcome. Liver Transpl. 2009;15:475–83. doi:10.1002/lt.21682.
129. Foxton MR, Al-Freah MAB, Portal AJ, Sizer E, Bernal W, Auzinger G, et al. Increased model for end-stage liver disease score at the time of liver transplant results in prolonged hospitalization and overall intensive care unit costs. Liver Transpl. 2010;16:668–77. doi:10.1002/lt.22027.
130. Bahirwani R, Reddy KR. Outcomes after liver transplantation: chronic kidney disease. Liver Transpl. 2009;15 Suppl 2:S70–4. doi:10.1002/lt.21900.
131. Cabezuelo JB, Ramírez P, Ríos A, Acosta F, Torres D, Sansano T, et al. Risk factors of acute renal failure after liver transplantation. Kidney Int. 2006;69:1073–80. doi:10.1038/sj.ki.5000216.

132. Ferreira AC, Nolasco F, Carvalho D, Sampaio S, Baptista A, Pessegueiro P, et al. Impact of RIFLE classification in liver transplantation. Clin Transplant. 2010;24:394–400. doi:10.1111/j.1399-0012.2009.01087.x.
133. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8:R204–12. doi:10.1186/cc2872.
134. O'Riordan A, Wong V, McQuillan R, McCormick PA, Hegarty JE, Watson AJ. Acute renal disease, as defined by the RIFLE criteria, post-liver transplantation. Am J Transplant. 2007;7:168–76. doi:10.1111/j.1600-6143.2006.01602.x.
135. Greig PD, Woolf GM, Abecassis M, Forster J, Strasberg SM, Taylor BR, et al. Prostaglandin E1 for primary nonfunction following liver transplantation. Transplant Proc. 1989;21: 3360–1.
136. Estrin JA, Belani KG, Ascher NL, Lura D, Payne W, Najarian JS. Hemodynamic changes on clamping and unclamping of major vessels during liver transplantation. Transplant Proc. 1989;21:3500–5.
137. Biancofiore G, Bindi L, Romanelli AM, Bisà M, Boldrini A, Consani G, et al. Renal failure and abdominal hypertension after liver transplantation: determination of critical intra-abdominal pressure. Liver Transpl. 2002;8:1175–81. doi:10.1053/jlts.2002.36246.
138. Niemann CU, Walia A, Waldman J, Davio M, Roberts JP, Hirose R, et al. Acute kidney injury during liver transplantation as determined by neutrophil gelatinase-associated lipocalin. Liver Transpl. 2009;15:1852–60. doi:10.1002/lt.21938.
139. Martin M, Neumann D, Hoff T, Resch K, DeWitt DL, Goppelt-Struebe M. Interleukin-1-induced cyclooxygenase 2 expression is suppressed by cyclosporin A in rat mesangial cells. Kidney Int. 1994;45:150–8.
140. Lee JP, Heo NJ, Joo KW, Yi NJ, Suh K-S, Moon KC, et al. Risk factors for consequent kidney impairment and differential impact of liver transplantation on renal function. Nephrol Dial Transplant. 2010;25:2772–85. doi:10.1093/ndt/gfq093.
141. Gibney N, Cerda J, Davenport A, Ramirez J, Singbartl K, Leblanc M, et al. Volume management by renal replacement therapy in acute kidney injury. Int J Artif Organs. 2008;31: 145–55.
142. Davenport A, Farrington K. Dialysis dose in acute kidney injury and chronic dialysis. Lancet. 2010;375:705–6. doi:10.1016/S0140-6736(09)62062-6.

Living Donor Liver Transplantation

10

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10.1 Introduction

Ever since its initial successful implementation in the clinical practice, liver transplantation has been plagued with a shortage of donor organs. The transplant community has responded by implementing proven strategies, including improved preservation techniques, refined surgical approaches enabling the use of expanded criteria donors (i.e., aged liver, steatotic grafts, and donation after cardiac death, DCD), and the introduction of adult partial liver transplantation (split liver and living donor liver transplantation). While the use of marginal grafts and split liver transplantation seems to have plateaued, living donor liver transplantation (LDLT) holds the greatest promise for an underutilized source of transplantable grafts. Since its introduction in 1988, thousands of pediatric and adult patients have been saved by LDLT, which is now embraced by transplant centers around the world. Over the course of almost two decades, tremendous effort has been given to improving donor safety while optimizing the outcome of recipients. Increasing sophistication of the preoperative donor workup, more liberal use of adult-to-adult left lobe liver transplantation, introduction of inflow modification, improved recipient selection, better understanding of small-for-size graft syndrome, and, most importantly, a more holistic approach to this complex practice have yielded acceptable donor morbidity and mortality rates along with excellent recipient outcomes.

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10.2 Indications to LDLT

Although the safety and effectiveness of LDLT for children are well established and accepted worldwide in part because of the severe shortage of pediatric deceased donor organs, the use of adult-to-adult LDLT varies depending on the availability of deceased donor organ pools [1]. In Asia, where most liver transplants are performed with live donors, LDLT is utilized for critically ill patients with high MELD scores. Conversely, in western countries with well-developed organ allocation systems and larger deceased donor organ pools, adult-to-adult LDLT is reserved mainly for patients with relatively low MELD scores. In these countries, the aggressive application of adult-to-adult LDLT is still controversial.

10.3 Donor Evaluation

10.3.1 General Overview of Donor Evaluation

In concert with the dictum of "primum non nocere," the evaluation of a potential living liver donor is the most important step to mitigate the risk of organ donation for someone who otherwise would not need surgery except this noble purpose. Donor evaluation involves medical, psychiatric, social, and sometimes genetic examinations. Potential donors with concomitant medical illness should not be accepted for living donation. A psychiatric evaluation is mandatory in most programs due to the complex emotional nature of the decision and the small, but documented, risk of donor suicide [2]. Genuine volunteerism can be confirmed with a thorough evaluation, including an interview with psychiatrist and other members of the donor advocacy team.

The upper age limit for live donation varies from 55 to 60 years. Donor age also can affect the quality of liver graft [3]. Some studies have reported that aged liver grafts are more susceptible to portal hyperperfusion and thus have a greater risk of small-for-size syndrome (SFSS) [4].

When the donor candidate is a relative of a recipient whose liver disease is either hereditary or due to an autoimmune disease, the donor should be screened for the presence of such conditions. These conditions include Wilson's disease, Alagille syndrome, polycystic liver disease, congenital hepatic fibrosis, and primary sclerosing cholangitis. Appropriate imaging and genetic study and/or liver biopsy may be needed to exclude potential donor with liver pathology.

Once the donor is deemed to be a good candidate from medical and psychosocial perspectives, the anatomical and surgical aspects should be carefully evaluated. Particularly, liver anatomy is the most critical element of surgical planning. Points to look for in the preoperative imaging studies include graft and remnant liver size and vascular and biliary anatomy. This evaluation process is not only indispensable for surgery but is also important for the possible exclusion of high-risk donors in surgical perspective.

Since hepatic macrosteatosis increases the morbidity and mortality in both recipient and donor, the assessment of hepatic macrosteatosis in the donor liver is imperative. Obese candidates are recommended to lose weight, thereby reducing hepatic

steatosis and the risk of postoperative morbidity, including deep venous thrombosis and respiratory complications. Ultrasound and CT are useful measures to evaluate hepatic steatosis.

The prevalence of nonalcoholic steatohepatitis (NASH) has been rapidly increasing in the general population; thus, attention should be paid for screening of NASH in donor candidates. One donor death was correlated with NASH in a small remnant donor liver [5]. NASH is frequently seen in people with metabolic syndrome, including those with glucose intolerance and obesity.

Liver biopsy may be performed on donor candidates to evaluate the degree of hepatic macrosteatosis or to rule out NASH. Indication of liver biopsy varies in each program. In our center we perform a liver biopsy on all donors with a BMI > 30.

10.4 Graft Selection

The vast majority of the living donor liver transplant programs consider three types of grafts: the left lateral segment (segments II and III), the left lobe (segments I–IV) with the middle hepatic vein, and the right lobe (segments V–VIII) without the middle hepatic vein. The left lateral segment represents 20–25 % of the total liver and is usually used for children. Among the three types of standard grafts, the left lateral segment is generally least harmful for living donors. The left lobe represents 30–40 % and is usually offered to teenagers or small adults. Finally, the right lobe accounts for 60–70 % and usually provides the most promising outcomes in the recipient. However, it contains a highest risk of significant morbidity and mortality in the donor.

When donor anatomy is not suitable for the abovementioned standard grafts, non-standard grafts can be used by an experienced transplant team. The extended right lobe graft with the middle hepatic vein provides a larger liver volume and better venous outflow in the recipient. However, this graft imposes a higher risk for the donor compared to the right lobe graft without the middle hepatic vein. When the donor has a disproportionately small left lobe and a rare anatomical variant of the portal vein and bile duct, the right posterior segment graft (segment VI–VII) sometimes can be used. However, this graft requires complex surgical techniques and is characterized by a high incidence of biliary complications [6]. In pediatric cases of body weight < 5 kg, a reduced left lateral segment graft is used to avoid large-for-size syndrome [7].

Two primary concepts are considered when determining the type of graft used in LDLT. Namely, consideration is given to the future liver remnant (FLR) and the graft to recipient body weight ratio (GRWR). The FLR is the proportion of remaining liver volume that stays in the donor after the partial graft is removed. A FLR of 30 % is considered to be an acceptable lower limit for donor hepatectomy. A FLR less than 30 % carries significant risk of developing postoperative liver failure for the donor. The GRWR is the ratio of the donor graft weight to the recipient body weight. The accepted lower limit of GRWR to avoid small-for-size-related complications is generally considered to be 0.8 % [8]. Many centers prefer to keep a GRWR of at least 1 % to secure a margin of safety for the recipient when recipient physiology is unfavorable for partial liver grafting, and technical complexities are

anticipated in the recipient surgery. While the GRWR can be reduced to 0.6 % in selected cases with active portal inflow modification, such a small graft still contains the higher risk of developing small-for-size-related graft failure.

10.4.1 Maximized Effort of Using Left Lobe Graft for Adult Recipients

Historically, left lobe grafts were first used in 1993 [9], followed a few years later by the larger right lobe grafts [10]. While the systematic utilization of right lobe grafts allowed for the rapid expansion of this technology with good outcomes in recipients, it soon became clear that there were more complications and mortalities in right lobe donors [11, 12]. The rate of complication following right lobectomy is two to four times greater compared to complications following left lobectomy [13, 14].

Figure 10.1 shows suggested algorithm of graft selection for adult recipients. If the left lobe provides a GRWR > 0.8 % or >40 % ELV/SLV, it is certainly the preferred graft. If the left lobe is calculated to provide 0.6–0.8 % GRWR or 30–40 % GV/SLV, alternative strategies need to be employed in patients with portal hypertension; however, these grafts are adequate for certain patients with no portal hypertension, such as those with metastatic neuroendocrine tumors. The strategies for utilizing smaller left lobe grafts for patients with portal hypertension involve dual grafting as described by Lee [15] and various techniques of inflow modulation as described above.

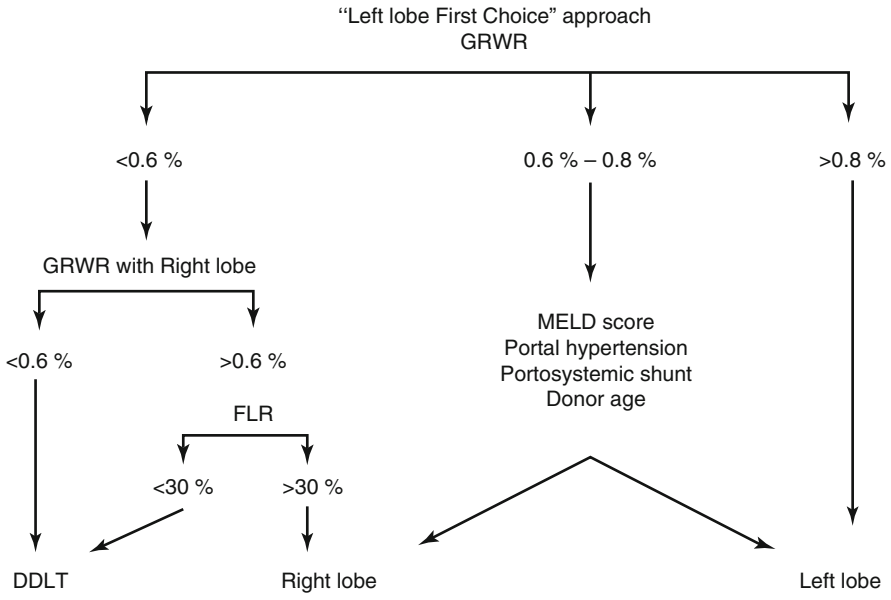

Fig. 10.1 Diagram showing our "left lobe first choice" approach. Every donor is first screened for a left living donor hepatectomy following this algorithm

10.5 State-of-the-Art Preoperative Planning

Preoperative planning is arguably the most important factor involved in optimal outcomes for both donors and recipients. A thorough preoperative planning process integrates information gained from donor vascular, biliary, and volumetric analyses and recipient clinical and hemodynamic data to establish the best donor-recipient combination.

10.5.1 Donor Anatomical Evaluation

The first step in the assessment of a potential donor is a standard triple phase CT scan of the abdomen. A 1–2 mm incremental reconstruction is performed in both the arterial and venous phases to provide a very detailed arterial and venous anatomy of the donor as well as a volumetric analysis of the left/right lobes and FLR. Most centers obtain a preoperative assessment of the bile duct anatomy using magnetic resonance cholangiopancreatography (MRCP). CT cholangiography and ERCPs have been abandoned almost universally because the IV contrast agent used to opacify the biliary tree carries a relatively high risk of allergic reaction [16] and because of the potential for ERCP-related complications [17]. Additionally, all donors undergo an intraoperative cholangiogram to determine the anatomical and bile duct transection line.

If the CT scan and the MRCP show no contraindication for living donor hepatectomy, the images are elaborated to obtain a 3D rendering of the liver along with its vascular and biliary components (in our institution images are sent to MEVIS distant service; Bremen, Germany). 3D reconstruction (Fig. 10.2) carries several advantages over bi-dimensional imaging. First, it allows the representation of the portal vein, hepatic artery, and the bile duct bifurcation in one fused three-dimensional image that can be viewed, rotated, and manipulated to best predict and simulate the perspective encountered during surgery. Second, 3D reconstruction simulates the parenchymal transaction line with superimposed vascular and biliary structures, improving the surgeon's ability to preoperatively understand the spatial relationships of these structures and therefore helps minimize intraoperative complications [18].

Additionally, 3D reconstruction provides an accurate assessment of the total and segmental liver volumes with a percentage of error of approximately 2.8 % [19, 20]. The estimated weight is obtained from volumes using a correction factor of 0.9 [21] and is used to calculate the estimated GRWR.

Finally, using a semi-automated process, 3D reconstruction depicts hepatic venous territories with the amount of parenchyma individually drained. This calculation is very important when making decisions about graft selection, inclusion/exclusion of the middle hepatic vein in the graft, and segmental venous reconstruction. These are all key functional aspects of partial graft transplantation, since suboptimal graft outflow is associated clearly with compromised regeneration, SFSS, and biliary complications [22, 23].

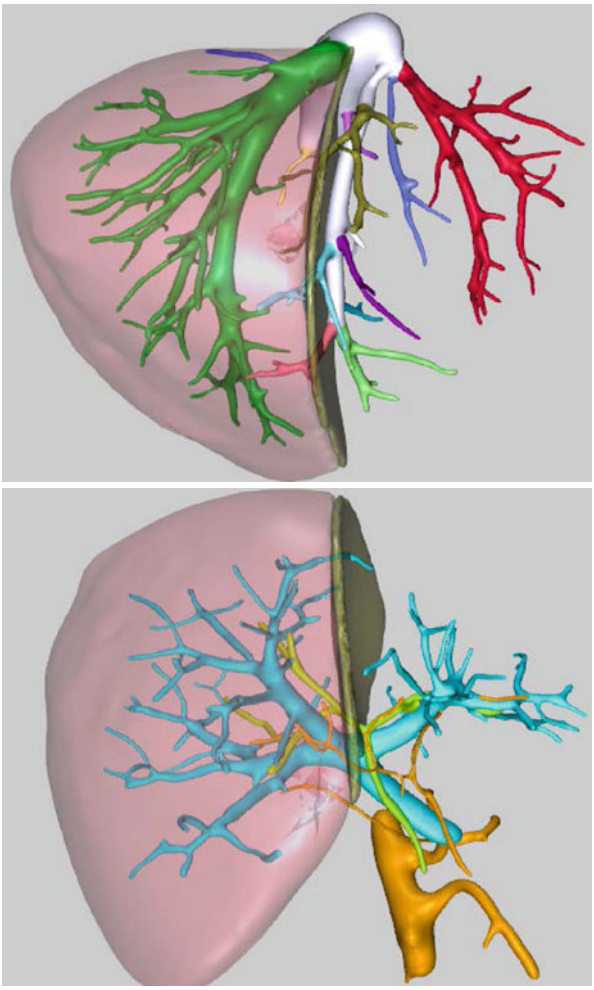

Fig. 10.2 MEVIS 3D reconstruction of the liver anatomy with proposed anatomical resection planes. Hepatic vein anatomy, combined portal vein, hepatic artery, and bile duct analysis

10.5.2 Innovations in Living Donor Preoperative Planning

10.5.2.1 3D Liver Printing

Three-dimensional (3D) printing is an innovative technology that produces solid objects starting from a digital image. Recently, our group was the first to describe [24] the use of this technology in LDLT. A total of six 3D-printed livers (three donors and three recipients) were analyzed prospectively and were found to be extremely accurate in depicting the spatial relationships and dimensions of the vascular and biliary structures of the actual livers (Fig. 10.3). 3D printing, though in its infancy, offers several theoretical advantages over the current 3D screen-only graft reconstruction. Importantly, having a physical model of the liver gives the surgeon a tool for intuitive navigation of the critical anatomical structures found during

surgery due to the transparency of the model and the use of color "ink" to print vascular and biliary structures. Future refinement of 3D printing and the modeling process may complement current imaging technology and provide surgeons with an additional planning tool.

10.5.2.2 Computer-Assisted Surgical Navigation

Computer-assisted surgery is used in numerous fields and only recently has been introduced in liver surgery. This technology involves the use of a tracking device and a computer system that integrates, in real time, the field position of the surgical instrument with the preoperative imaging of the patient. The tracked instrument position is overlaid on multiple CT/MRI images, improving the surgeon's spatial understanding of the vital structures that will be encountered during parenchymal dissection, thereby helping to minimize complications. While tracked surgical devices hold great potential in LDLT, the lack of accuracy during mobilization and repositioning of the liver is a current and significant limitation.

10.5.3 Recipient Evaluation

In order to optimize donor and recipient outcomes, preoperative donor assessments need to be integrated with recipient imaging and clinical information.

The recipient's clinical characteristics, such as MELD score, severity of portal hypertension, and hemodynamic parameters (CO, CI), are combined with imaging data, including spleen dimension and the presence of portosystemic shunts to guide

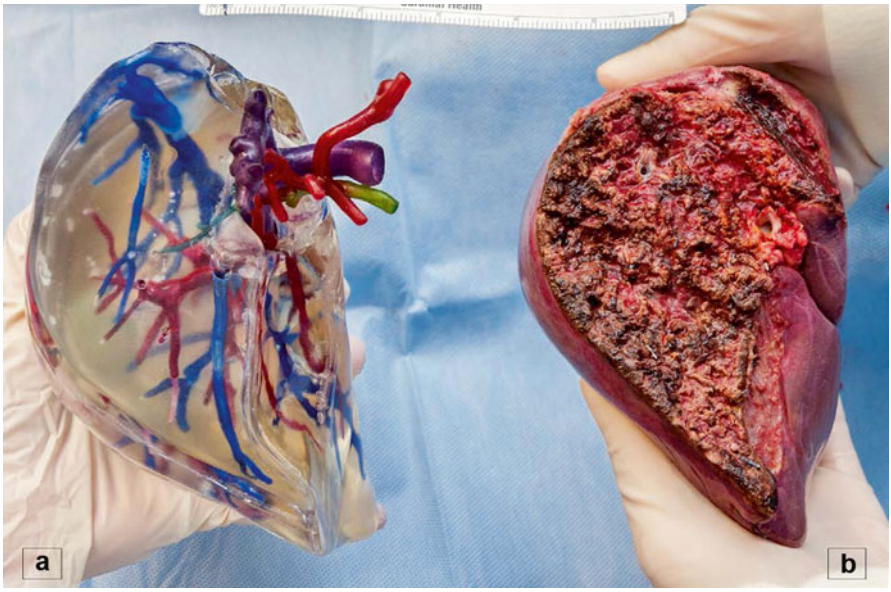

Fig. 10.3 3D printed right hemiliver (**a**) with the respective graft (**b**)

the choice of the graft. High-risk patients, such as those with a high MELD score or severe portal hypertension, should be considered for LDLT only if a GRWR > 0.8 can be safely obtained. Conversely, recipients with large portosystemic shunts and therefore decompressed portal venous system can be considered for smaller grafts, ideally left lobe.

10.6 Surgical Techniques

10.6.1 Graft Type and Surgical Planning

10.6.1.1 Donor Surgery

Unlike liver resection for malignancy, both portions of the graft and the remnant liver must be handled with extreme caution in donor hepatectomy. Preservation of vascular and biliary integrity on both sides of the liver is critical. Donor safety depends on preoperative knowledge of surgical anatomy, which is highly variable. The presence of multiple variants may be a relative contraindication for donation, particularly in high-risk cases.

Several important principles must be followed in donor surgery to maximize donor safety. First, contralateral hepatic ligaments should not be divided. The division of these ligaments can cause malrotation of the remnant liver, which in turn may cause catastrophic vascular insufficiency in the donor. Second, an intraoperative cholangiogram should be performed before hilar dissection to rule out anatomical variants that are not found preoperatively. Third, hepatic hilar dissection on the side of the hepatic lobe or segment should be minimized to avoid compromising blood supply to the bile duct. Fourth, a confirmatory cholangiogram should be performed after the graft liver is removed to confirm the integrity of the biliary system. Fifth, after a right hepatectomy, the falciform ligament should be tagged to the anterior abdominal wall to avoid malrotation of the remnant liver. In addition to these, the use of the liver hanging maneuver helps minimize blood loss and guides the direction of parenchymal transection [25]. Liver parenchymal division should be performed with familiar methods (CUSA, clamp-crushing technique, water-jet, bipolar coagulator, etc.) that further help minimize blood loss.

While experienced centers have performed donor hepatectomy through minimally invasive techniques, general application of this approach remains controversial due to concerns about the difficulty of controlling inadvertent massive bleeding under a laparoscopic view. Furthermore, surgical stress on living donors seems to be determined by the amount of liver mass removed during donor surgery rather than the size of incisions. Therefore, further studies and extensive discussion will be necessary before reaching a general consensus on minimally invasive donor hepatectomy.

The extent of venous reconstruction varies considerably between the left and the right lobe. The left lobe graft usually needs a simple venoplasty to optimize venous outflow on the back table [26]. In contrast, the right lobe graft frequently needs complex venous reconstruction. Reconstruction of segment five and eight veins increases the functional liver mass so that it is comparable to the extended right lobe graft with the middle hepatic vein. Vascular grafts for this reconstruction can be

taken from unused vessels procured from deceased donors, cryopreserved grafts, and autologous veins such as recipient intrahepatic portal vein, internal jugular vein, and recanalized umbilical vein [27]. If these grafts are not available, expanded polytetrafluoroethylene grafts can be used with excellent early patency [28]. When two separate hepatic ducts are identified, these can be combined together using a ductoplasty technique to avoid multiple biliary reconstructions in the recipient.

10.6.1.2 Recipient Surgery

Two major components of recipient surgery are essential to achieve good outcomes: excellent venous outflow to prevent graft congestion and active portal inflow modification to optimize graft hemodynamics. In the small pediatric cases, venous outflow can be maximized by making a vertical cavotomy on the retrohepatic cava from the common orifice of the three hepatic veins to create a triangular shape orifice [29]. This technique was first described in 1988, but remains the gold standard of outflow venous reconstruction in pediatric partial grafting. This technique can also be applied for the left lobe graft in adults. If the recipient venous orifice is too big and does not match the donor hepatic vein, the alternative technique for left lobe venous reconstruction is to make a horizontal cavotomy on the right side of the middle hepatic vein to enlarge the size of the common channel of the left and middle hepatic veins. In the right lobe graft, multiple venous anastomoses are frequently required, including the right hepatic veins and anterior segment branches. When a venous patch is available, multiple venous orifices can be combined together to perform one-step venous anastomosis [30]. Suboptimal venous outflow decreases functional graft size and increases the risk of graft dysfunction or failure.

In size-mismatch adult LDLT, a small graft receives excessive portal flow causing an arterial spasm via hepatic arterial buffer response, which explains the pathophysiology of SFSS [31]. Splenic artery ligation is the most frequently used technique for inflow modulation, but the effect of portal flow reduction is not always promising. Splenectomy is more effective but less frequently used due to the risk of increased blood loss and post-splenectomy sepsis [32]. Portosystemic shunt continues to be used by some centers with excellent outcomes, but there is an increased risk of portal flow steal resulting in graft hypoperfusion [33].

10.7 Recipient Outcomes

In pediatric patients, graft and patient survival is comparable or better for LDLT than deceased donor liver transplantation. This result is consistent with the historical observation in split liver transplantation using deceased donors. In LDLT for adults, national data in the USA has shown that the outcomes in LDLT are comparable to deceased donor liver transplantation in terms of survival, cost, and hospital mortality, despite the increased risk of early complications [34]. Moreover, an intent-to-treat analysis has proved a significant survival benefit of recipients who received livers from living donors compared to deceased donors [35, 36].

Interestingly, the outcome advantage for LDLT is sustained even for those recipients with a MELD score of <15 [37], a group that generally does not benefit from DDLT.

10.7.1 Hepatocellular Carcinoma

Early studies raised the concern that the high regeneration rate of LDLT grafts early after transplant could induce HCC and HCV recurrence. A single-center study showed higher tumor recurrence rate after LDLT compared to that of DDLT [38]. Recently, a multicenter study by the A2ALL group confirmed the finding [39]. The study suggested that the higher recurrence rate was due to advanced staged tumors in the LDLT group. More specifically, the shorter waiting period between diagnosis or locoregional therapy and LDLT seemed to allow recipients with aggressive HCC to undergo LDLT. The longer waiting time for DDLT seemed to result in a pool of transplant recipients who had less aggressive tumors. Interestingly, the study suggested a mandated observation time after locoregional therapy before LDLT for recipients with advanced HCC in order to determine tumor biological behavior and to exclude candidates with aggressive HCC who likely would not benefit from LDLT. The study suggests that such an approach would result in comparable outcomes following both LDLT and DDLT for HCC.

10.7.2 Hepatitis C

HCV cirrhosis is the important indication for both DDLT and LDLT. While early data suggested that HCV may recur earlier and the incidence of severe recurrence is higher for HCV patients undergoing LDLT [40, 41], recent studies demonstrate that the outcome is approximately equal to that of DDLT [42].

10.8 Complications

10.8.1 Donor Complications

To date, more than 11,500 LDLTs have been performed worldwide with a total of 34 living liver donor deaths reported in the literature [43]. A longitudinal observational cohort of 740 living donor hepatectomies (707 right/33 left hepatectomies) performed at nine major US centers (A2ALL consortium) [43] experienced an overall complications rate of 40 %, with a 1 % incidence of catastrophic complications (residual disability, liver failure, or death) and 2–5 % risk of aborted donation. These complication rates were confirmed by other groups [44, 45]. Infections represented the most common complication (10 %). Bile leak/biloma accounted for 8 % of complications, followed by incisional hernia 6 %, psychological complications 6 %, neuropraxia 3 %, ileus 3 %, unplanned re-exploration 2 %, ascites 2 %, pleural effusion 1.8 %, bowel obstruction 1.6 %, DVT/pulmonary embolism 1.5 %, intra-abdominal abscess 1 %, intra-abdominal bleeding 0.9 %, and biliary stricture 0.6 %. Based on the existing literature, the risk of donor death after a right hepatectomy is 0.4–0.6 % and for a left-sided hepatectomy is 0.1–0.4 %.

10.8.2 Recipient Complications

Given its technical complexity, it is not surprising that LDLT carries higher complication rates compared to DDLT. Biliary complications remain the Achilles heel of LDLT, and most of the technical complications occur in the first 90 days after transplantation.

In a report of 385 transplants performed in the USA [46], early bile leaks were seen in 30 % of recipients, and biliary strictures were observed in 8 %. Vascular complications occurred in 8 % of patients (HAT 6 %, PV thrombosis 2 %). Intra-abdominal bleeding presented in 7 % of the patients, and a re-exploration was needed in 24 % of the cases. As center experience increased, the rate of biliary complications decreased from 38 % (first 20 cases) to 24 %. A similar trend was found in the rate of hepatic artery thrombosis 8–4 % and PV thrombosis (3–1 %). Biliary stricture (10 %), infections (8 %), and hernias (5 %) represented the most common complications after 90 days.

10.9 Strategy for ABO Incompatible LDLT

Generally, ABO-incompatible (ABOi) liver transplantation is contraindicated for deceased donor liver transplantation due to the high risk of graft loss resulting from antibody-mediated rejection (AMR) and vascular thrombosis. However, this immunological barrier can be overcome by desensitizing the recipient preoperatively in LDLT [3, 47].

Early experience of ABOi LDLT demonstrated devastating outcomes with a 1-year survival rate of 20 % in adult cases, while the survival of pediatric recipients <1 year old was comparable to that of compatible or identical blood combination [3].

Japanese groups introduced a desensitization protocol using the combination of anti-CD20 antibody (rituximab) and local infusion of anti-inflammatory agents into the graft through portal vein or hepatic artery, achieving significantly improved outcomes [48, 49]. In 2008, the Japanese registry for ABOi LDLT reported the largest experience of 291 recipients who received ABOi grafts [47]. Interestingly, high preoperative antibody titer did not have a significant effect on the frequency of AMR. In contrast, elevated postoperative anti-donor blood-type antibody titer increases the risk for AMR.

The significant effect of rituximab raised a question whether local infusion is necessary with a high rate of catheter-related lethal complications such as hepatic infarction and catheter dislocation [47, 50]. The Asan group reported 120 ABOi adult LDLT using the desensitization protocol using rituximab and plasmapheresis with ($n = 20$) or without local infusion ($n = 100$) [51]. The results were promising with an overall graft survival rate of 92.8 % at 3 years. Although the study showed a high incidence of catheter-related complication (30 %), there were no significant outcome differences between the two groups in terms of the rate of AMR and acute cellular rejection as well as graft and patient survival.

10.10 Preparing for the Worst-Case Scenario: The Death of a Living Liver Donor

LDLT is associated with a low, yet well-defined, risk of donor morbidity and mortality. It is therefore crucial that centers and institutions involved in this activity acknowledge the fact that the death of a living donor is as a matter of "when" rather than "if" [52]. Countless studies in the field of risk management show that "preparing for the inevitable" not only is critical in better preparing teams to respond to catastrophic events, but also plays a key role in their prevention. Therefore, LDLT programs must implement strategies and protocols to assure that such events are carefully anticipated and properly managed, should they occur [52]. The more "immune" a LDLT program thinks it is to the death of a living donor, the less it prepares for and the more vulnerable it becomes.

References

1. Fan ST. Live donor liver transplantation in adults. Transplantation. 2006;82(6):723–32.
2. Cheah YL, Simpson MA, Pomposelli JJ, Pomfret EA. Incidence of death and potentially life-threatening near-miss events in living donor hepatic lobectomy: a world-wide survey. Liver Transpl. 2013;19(5):499–506.
3. Kiuchi T, Inomata Y, Uemoto S, Asonuma K, Egawa H, Fujita S, et al. Evolution of living donor liver transplantation in adults: a single center experience. Transpl Int. 2000;13(Suppl 1): S134–5.
4. Sanefuji K, Iguchi T, Ueda S, Nagata S, Sugimachi K, Ikegami T, et al. New prediction factors of small-for-size syndrome in living donor adult liver transplantation for chronic liver disease. Transpl Int. 2010;23(4):350–7.
5. Akabayashi A, Slingsby BT, Fujita M. The first donor death after living-related liver transplantation in Japan. Transplantation. 2004;77(4):634.
6. Yoshizumi T, Ikegami T, Kimura K, Uchiyama H, Ikeda T, Shirabe K, et al. Selection of a right posterior sector graft for living donor liver transplantation. Liver Transpl. 2014;20(9): 1089–96.
7. Kanazawa H, Sakamoto S, Fukuda A, Uchida H, Hamano I, Shigeta T, et al. Living-donor liver transplantation with hyperreduced left lateral segment grafts: a single-center experience. Transplantation. 2013;95(5):750–4.
8. Selzner M, Kashfi A, Cattral MS, Selzner N, Greig PD, Lilly L, et al. A graft to body weight ratio less than 0.8 does not exclude adult-to-adult right-lobe living donor liver transplantation. Liver Transpl. 2009;15(12):1776–82.
9. Hashikura Y, Makuuchi M, Kawasaki S, Matsunami H, Ikegami T, Nakazawa Y, et al. Successful living-related partial liver transplantation to an adult patient. Lancet. 1994;343(8907):1233–4.
10. Lo CM, Fan ST, Liu CL, Wei WI, Lo RJ, Lai CL, et al. Adult-to-adult living donor liver transplantation using extended right lobe grafts. Ann Surg. 1997;226(3):261–9; discussion 9–70.
11. Hwang S, Lee SG, Lee YJ, Sung KB, Park KM, Kim KH, et al. Lessons learned from 1,000 living donor liver transplantations in a single center: how to make living donations safe. Liver Transpl. 2006;12(6):920–7.
12. Ghobrial RM, Freise CE, Trotter JF, Tong L, Ojo AO, Fair JH, et al. Donor morbidity after living donation for liver transplantation. Gastroenterology. 2008;135(2):468–76.
13. Umeshita K, Fujiwara K, Kiyosawa K, Makuuchi M, Satomi S, Sugimachi K, et al. Operative morbidity of living liver donors in Japan. Lancet. 2003;362(9385):687–90.

14. Hashikura Y, Ichida T, Umeshita K, Kawasaki S, Mizokami M, Mochida S, et al. Donor complications associated with living donor liver transplantation in Japan. Transplantation. 2009;88(1):110–4.
15. Lee SG. A complete treatment of adult living donor liver transplantation: a review of surgical technique and current challenges to expand indication of patients. Am J Transplant. 2014;15:17–38.
16. Nilsson U. Adverse reactions to iotroxate at intravenous cholangiography. A prospective clinical investigation and review of the literature. Acta Radiol. 1987;28(5):571–5.
17. Masci E, Toti G, Mariani A, Curioni S, Lomazzi A, Dinelli M, et al. Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. Am J Gastroenterol. 2001;96(2):417–23.
18. Endo I, Shimada H, Sugita M, Fujii Y, Morioka D, Takeda K, et al. Role of three-dimensional imaging in operative planning for hilar cholangiocarcinoma. Surgery. 2007;142(5):666–75.
19. Pomposelli JJ, Tongyoo A, Wald C, Pomfret EA. Variability of standard liver volume estimation versus software-assisted total liver volume measurement. Liver Transpl. 2012;18(9):1083–92.
20. Satou S, Sugawara Y, Tamura S, Yamashiki N, Kaneko J, Aoki T, et al. Discrepancy between estimated and actual weight of partial liver graft from living donors. J Hepatobiliary Pancreat Sci. 2011;18(4):586–91.
21. Kim KW, Lee J, Lee H, Jeong WK, Won HJ, Shin YM, et al. Right lobe estimated blood-free weight for living donor liver transplantation: accuracy of automated blood-free CT volumetry–preliminary results. Radiology. 2010;256(2):433–40.
22. Akamatsu N, Sugawara Y, Kaneko J, Sano K, Imamura H, Kokudo N, et al. Effects of middle hepatic vein reconstruction on right liver graft regeneration. Transplantation. 2003;76(5):832–7.
23. Lee S, Park K, Hwang S, Lee Y, Choi D, Kim K, et al. Congestion of right liver graft in living donor liver transplantation. Transplantation. 2001;71(6):812–4.
24. Zein NN, Hanouneh IA, Bishop PD, Samaan M, Eghtesad B, Quintini C, et al. Three-dimensional print of a liver for preoperative planning in living donor liver transplantation. Liver Transpl. 2013;19(12):1304–10.
25. Ogata S, Belghiti J, Varma D, Sommacale D, Maeda A, Dondero F, et al. Two hundred liver hanging maneuvers for major hepatectomy: a single-center experience. Ann Surg. 2007;245(1):31–5.
26. Suehiro T, Shimada M, Kishikawa K, Shimura T, Soejima Y, Yoshizumi T, et al. Impact of graft hepatic vein inferior vena cava reconstruction with graft venoplasty and inferior vena cava cavoplasty in living donor adult liver transplantation using a left lobe graft. Transplantation. 2005;80(7):964–8.
27. Ikegami T, Soejima Y, Taketomi A, Yoshizumi T, Harada N, Uchiyama H, et al. Explanted portal vein grafts for middle hepatic vein tributaries in living-donor liver transplantation. Transplantation. 2007;84(7):836–41.
28. Yi NJ, Suh KS, Lee HW, Cho EH, Shin WY, Cho JY, et al. An artificial vascular graft is a useful interpositional material for drainage of the right anterior section in living donor liver transplantation. Liver Transpl. 2007;13(8):1159–67.
29. Broelsch CE, Emond JC, Thistlethwaite JR, Whitington PF, Zucker AR, Baker AL, et al. Liver transplantation, including the concept of reduced-size liver transplants in children. Ann Surg. 1988;208(4):410–20.
30. Soejima Y, Ueda N, Fukuhara T, Yoshizumi T, Ikegami T, Yamashita Y, et al. One-step venous reconstruction for a right lobe graft with multiple venous orifices in living donor liver transplantation. Liver Transpl. 2008;14(5):706–8.
31. Kelly DM, Zhu X, Shiba H, Irefin S, Trenti L, Cocieru A, et al. Adenosine restores the hepatic artery buffer response and improves survival in a porcine model of small-for-size syndrome. Liver Transpl. 2009;15(11):1448–57.

32. Yoshizumi T, Taketomi A, Soejima Y, Ikegami T, Uchiyama H, Kayashima H, et al. The beneficial role of simultaneous splenectomy in living donor liver transplantation in patients with small-for-size graft. Transpl Int. 2008;21(9):833–42.
33. Botha JF, Langnas AN, Campos BD, Grant WJ, Freise CE, Ascher NL, et al. Left lobe adult-to-adult living donor liver transplantation: small grafts and hemiportocaval shunts in the prevention of small-for-size syndrome. Liver Transpl. 2010;16(5):649–57.
34. Hoehn RS, Wilson GC, Wima K, Hohmann SF, Midura EF, Woodle ES, et al. Comparing living donor and deceased donor liver transplantation: a matched national analysis from 2007 to 2012. Liver Transpl. 2014;20(11):1347–55.
35. Berg CL, Gillespie BW, Merion RM, Brown Jr RS, Abecassis MM, Trotter JF, et al. Improvement in survival associated with adult-to-adult living donor liver transplantation. Gastroenterology. 2007;133(6):1806–13.
36. Berg CL, Merion RM, Shearon TH, Olthoff KM, Brown Jr RS, Baker TB, et al. Liver transplant recipient survival benefit with living donation in the model for endstage liver disease allocation era. Hepatology. 2011;54(4):1313–21.
37. Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant. 2005;5(2):307–13.
38. Kulik L, Abecassis M. Living donor liver transplantation for hepatocellular carcinoma. Gastroenterology. 2004;127(5 Suppl 1):S277–82.
39. Kulik LM, Fisher RA, Rodrigo DR, Brown Jr RS, Freise CE, Shaked A, et al. Outcomes of living and deceased donor liver transplant recipients with hepatocellular carcinoma: results of the A2ALL cohort. Am J Transplant. 2012;12(11):2997–3007.
40. Zimmerman MA, Trotter JF. Living donor liver transplantation in patients with hepatitis C. Liver Transpl. 2003;9(11):S52–7.
41. Garcia-Retortillo M, Forns X, Llovet JM, Navasa M, Feliu A, Massaguer A, et al. Hepatitis C recurrence is more severe after living donor compared to cadaveric liver transplantation. Hepatology. 2004;40(3):699–707.
42. Shiffman ML, Stravitz RT, Contos MJ, Mills AS, Sterling RK, Luketic VA, et al. Histologic recurrence of chronic hepatitis C virus in patients after living donor and deceased donor liver transplantation. Liver Transpl. 2004;10(10):1248–55.
43. Roll GR, Parekh JR, Parker WF, Siegler M, Pomfret EA, Ascher NL, et al. Left hepatectomy versus right hepatectomy for living donor liver transplantation: shifting the risk from the donor to the recipient. Liver Transpl. 2013;19(5):472–81.
44. Adcock L, Macleod C, Dubay D, Greig PD, Cattral MS, McGilvray I, et al. Adult living liver donors have excellent long-term medical outcomes: the University of Toronto liver transplant experience. Am J Transplant. 2010;10(2):364–71.
45. Iida T, Ogura Y, Oike F, Hatano E, Kaido T, Egawa H, et al. Surgery-related morbidity in living donors for liver transplantation. Transplantation. 2010;89(10):1276–82.
46. Olthoff KM, Merion RM, Ghobrial RM, Abecassis MM, Fair JH, Fisher RA, et al. Outcomes of 385 adult-to-adult living donor liver transplant recipients: a report from the A2ALL consortium. Ann Surg. 2005;242(3):314–23; discussion 23–5.
47. Egawa H, Teramukai S, Haga H, Tanabe M, Fukushima M, Shimazu M. Present status of ABO-incompatible living donor liver transplantation in Japan. Hepatology. 2008;47(1):143–52.
48. Tanabe M, Shimazu M, Wakabayashi G, Hoshino K, Kawachi S, Kadomura T, et al. Intraportal infusion therapy as a novel approach to adult ABO-incompatible liver transplantation. Transplantation. 2002;73(12):1959–61.
49. Nakamura Y, Matsuno N, Iwamoto H, Yokoyama T, Kuzuoka K, Kihara Y, et al. Successful case of adult ABO-incompatible liver transplantation: beneficial effects of intrahepatic artery infusion therapy: a case report. Transplant Proc. 2004;36(8):2269–73.
50. Ikegami T, Taketomi A, Soejima Y, Yoshizumi T, Uchiyama H, Harada N, et al. Rituximab, IVIG, and plasma exchange without graft local infusion treatment: a new protocol in ABO incompatible living donor liver transplantation. Transplantation. 2009;88(3):303–7.

51. Song GW, Lee SG, Hwang S, Ahn CS, Kim KH, Moon DB, et al. A desensitizing protocol without local graft infusion therapy and splenectomy is a safe and effective method in ABO-incompatible adult LDLT. Transplantation. 2014;97 Suppl 8:S59–66.
52. Miller C, Smith ML, Fujiki M, Uso TD, Quintini C. Preparing for the inevitable: the death of a living liver donor. Liver Transpl. 2013;19(6):656–60.

Liver

11

Francesco Vasuri, Deborah Malvi, and Antonia D'Errico

11.1 Pre-transplant Evaluation of the Donor Liver

Although not all centres still agree, histological evaluation of liver graft quality is crucial for the short-term outcome of orthotopic liver transplantation (OLT). Pre-transplant and "time zero" biopsies are useful for the assessment of macrovesicular steatosis, i.e. the histological alteration universally accepted as the major cause of early graft failure. Donor biopsies also provide information on graft preservation, fibrosis, and the occurrence of disregarded hepatitis or focal lesions.

The material sent to the pathologist should always include a wedge resection and a core biopsy. The final diagnosis should be made on the balance between them: the wedge resection includes more portal tracts, but the subcapsular localization increases the fibrosis and the inflammatory infiltrate [1]. Frozen-section analysis is considered the approach of choice for the evaluation of liver biopsies from cadaveric donors, both on economic and time-effective grounds [2]. Freezing the samples increases the risk of overestimating microvesicular steatosis due to the formation of intracellular droplets of frozen water. Nonetheless, the microsteatosis score is generally not used as a donor exclusion criterion, and this artifact can be ruled out by avoiding excessive soaking in saline solution or other media and transporting the biopsy in dry gauze or empty vials [1].

Suggested checklist for histopathological evaluation of the donor liver:

- Architecture and fibrosis assessment
- Portal inflammatory infiltrate: grade of inflammation and extension (little/most portal tract)

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- Bile duct status, including biliocyte regression and ductular proliferation
- Artery status, in particular the presence and amount of myointimal hypertrophy
- Lobules: occurrence and amount of lobular necrosis and/or inflammatory infiltrate
- Cholestasis
- Percentage of macrovesicular and microvesicular steatosis

This checklist offers the transplant team a quick and complete overview of graft status. In any case, it should be kept in mind that only macrovesicular steatosis has a proven higher risk of graft failure, and macrovesicular steatosis >30 % is generally a contraindication to OLT [3, 4] (Fig. 11.1). Other findings such as lobular necrosis and diffuse fibrosis can influence the decision to proceed, although there are currently no standardized indications.

11.2 Graft Dysfunction

11.2.1 Preservation Injury

Also called "ischaemia/reperfusion injury", preservation injury is the leading cause of early graft dysfunction and is defined as tissue damage occurring immediately after graft reperfusion, in the absence of other explicable causes of liver injury (e.g. vascular or biliary; see below).

The histopathological features of preservation injury depend on when the damage takes place: a warm ischaemia time of 120 min or more compromises both hepatocytes and endothelial cells, while a prolonged (usually more than 12 h) cold ischaemia is characterized by sinusoidal and endothelial damage, with a higher incidence of biliary complications [5, 6]. The reperfusion phase is the most crucial for the onset of liver preservation damage, since the reoxygenation after ischaemia causes activation of the Kupffer cells and complement factors, resulting in the production of reactive oxygen species and cytokines. The short-term consequences are granulocyte migration in the sinusoids and general vasoconstriction that can lead to graft circulatory failure [7].

Histopathology (Figs. 11.2 and 11.3) Microscopically, mild preservation injuries are visible on biopsies taken 1 h after OLT as microvesicular steatosis with hepatocyte swelling, but these features are rapidly reversible. Conversely, the more severe forms of preservation injury are characterized microscopically by hepatocyte necrosis, especially in zone 3, with acidophilic bodies and/or zonal or confluent necrosis. The adjacent viable hepatocytes can show ballooning and mitotic activity. Bile duct degeneration is visible as a detachment of the biliocytes from the basement membrane and as a ductular reaction with ductular and lobular neutrophilic infiltrate [8, 9]. As a consequence, both intracellular and extracellular cholestases (with bile plugs) are common. Cholestasis, architectural lobular distortion, hepatocyte mitotic activity with nuclear polymorphism and ballooning, as well as histiocytosis in zone 3 can be seen several weeks after OLT.

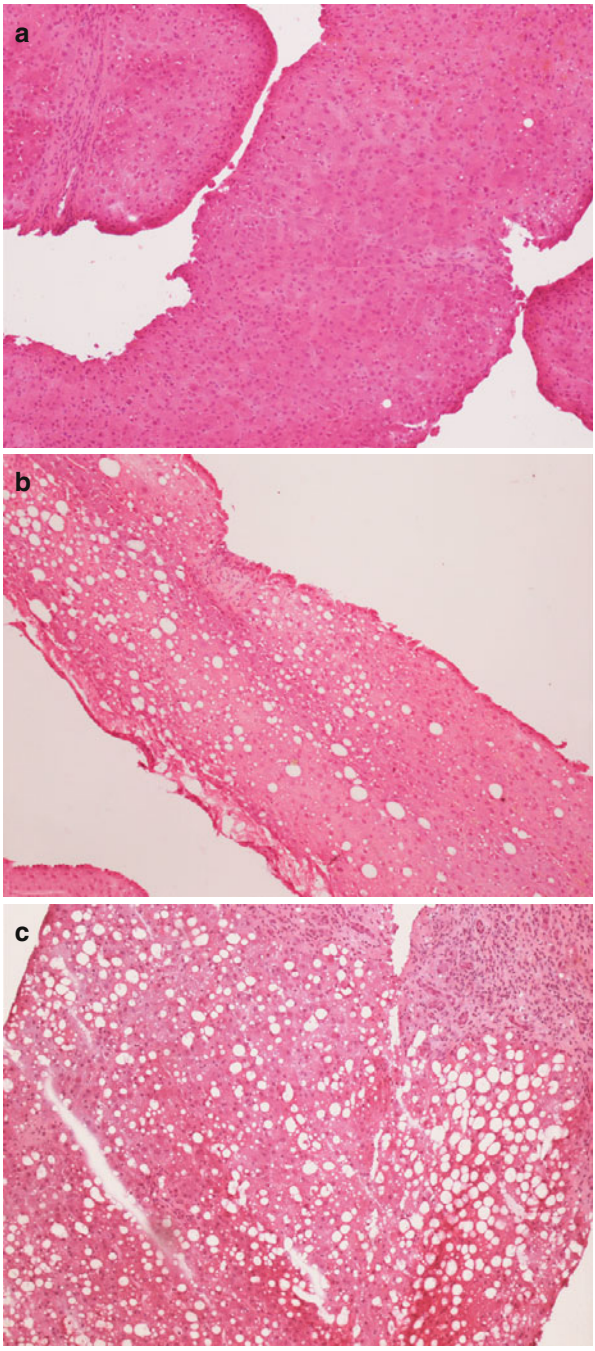

Fig. 11.1 Three examples of frozen-section analysis on donor liver biopsies with 0 % (**a**), 10 % (**b**) and >30 % (**c**) steatosis. In (**b**, **c**) freezing artifacts are visible as empty spaces, representing a pitfall in the evaluation of macrosteatosis. Magnification 10×

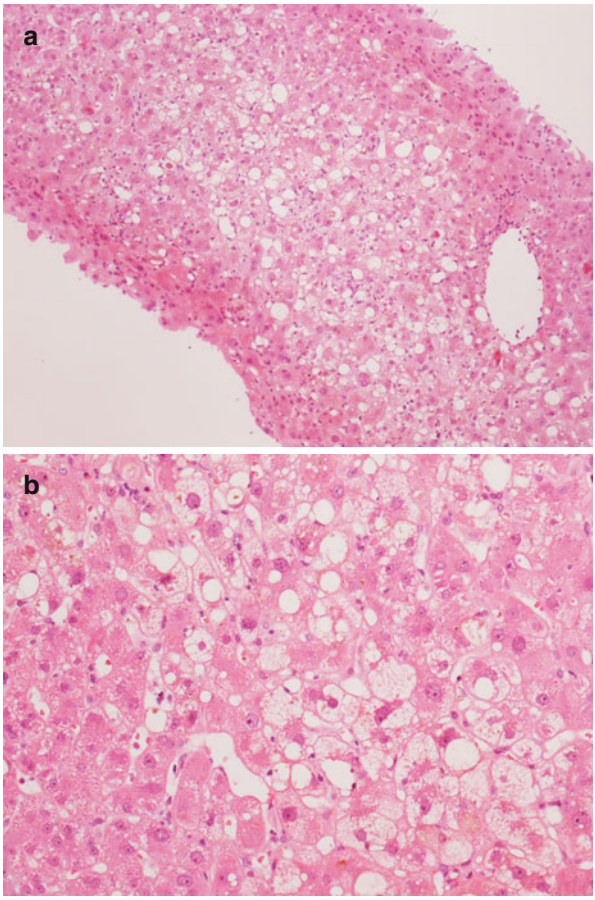

Fig. 11.2 (**a**, **b**) Ischaemic lobular damage, characterized by hepatocyte swelling and ballooning, without a significant inflammatory infiltrate. Magnification 10× (**a**); 20× (**b**)

Differential Diagnosis In these early phases, the differential diagnosis includes acute infections, biliary complications, and antibody-mediated rejection. Cholangitis, bile duct obstruction, and reperfusion injury share predominant zone 3 damage, but cholangitis is commonly characterized by periductal oedema with neutrophilic granulocytes [9]. Interestingly, immunohistochemical positivity for C4d has been demonstrated in necrosis during reperfusion injury [10].

11.2.2 Hyperperfusion ("Small-for-Size" Syndrome)

This is a very early post-transplant complication (within 2 weeks), due to inadequate graft size (less than 0.8 % of the recipient's weight) resulting in hyperdynamic portal flow. Allograft hyperperfusion is a critical condition that generally requires retransplantation.

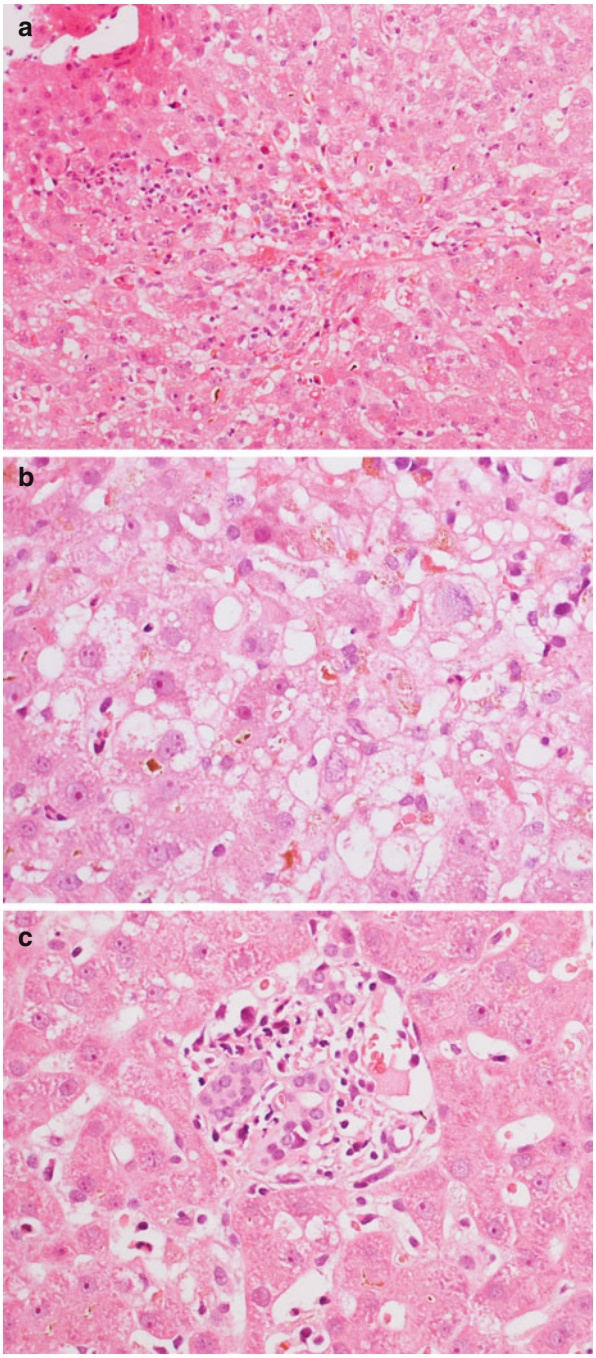

Fig. 11.3 (**a**) In some cases of ischaemia/reperfusion injury, architectural distortion, lobular haemorrhage with hepatocyte polymorphism and ballooning are visible. (**b**) Cholestasis and histiocytosis in zone 3 can be seen several weeks after OLT, associated with (**c**) portal tract distortion and bile duct regression. Magnification 20× (**a**); 40× (**b**, **c**)

Histopathology The histopathological modifications of "small-for-size" syndrome are commonly sorted into early, intermediate and late changes [11]. Starting from a few minutes after reperfusion, denudation of portal veins and sinusoids can be seen, resulting in haemorrhages in the periportal zone (zone 1), all consequences of portal hyperperfusion. In the more severe cases, ischaemic bile duct damage with lobular infarcts can be seen [9]. Intermediate features include hypertrophic changes in the endothelia, oedema and fibrosis, while the late changes comprise thrombosis and obliteration of the portal veins with recanalization, together with nodular regenerative hyperplasia and biliary stenosis.

Differential Diagnosis Arterial vascular complications (see below).

11.2.3 Vascular Complications

Post-OLT vascular complications include hepatic artery thrombosis, portal vein thrombosis and hepatic venous outflow obstruction (HVOO). Vascular complications represent a major technical problem after OLT and an important cause of liver damage and dysfunction in the first months after transplantation. Since liver biopsy is neither reliable nor safe in this setting, and the affected vascular structures are hilar and perihilar, histopathological examination is generally confined to the graft explant specimen [9].

Histopathology At gross examination, the liver surface may be normal, while foci of cholestasis and/or necrosis can be seen in some cases. At histology, thrombosis of the hepatic artery leads to ischaemic necrosis of the bile ducts with epithelial denudation and bile leakage into the surrounding parenchyma. Lobular alterations, ranging from Councilman's bodies to confluent hepatocytic necrosis, appear in the more severe and advanced cases. Prolonged arterial ischaemic injury can result in biliary strictures and fibrosis [12].

Histopathological examination of an allograft with portal vein thrombosis shows various degrees of parenchymal damage, from hepatocyte swelling and necrosis with haemorrhage and eventually thrombosis in the areas around the portal branches, to a pan-lobular necrosis of the allograft in cases with massive portal thrombosis. Chronic portal obstruction leads to nodular regenerative hyperplasia or similar changes [9].

HVOO can be due to problems at different levels, from congestive heart failure to Budd-Chiari syndrome and veno-occlusive disease affecting the portal venules or even sinusoids. The clinical presentations and the aetiologies of these conditions vary widely, but the histopathological picture is common. The first alterations affect the centrolobular zone (zone 3), with sinusoidal dilatation and centrolobular haemorrhage (in advanced cases), hepatocyte atrophy and loss of lobular architecture. Lobular or portal inflammation is lacking, and only the most severe cases show cholestasis. Chronicization (e.g. in Budd-Chiari syndrome, which is often subacute) leads to bridging fibrosis and the formation of hepatocellular nodules resembling focal nodular hyperplasia [12].

11.2.4 Large Bile Duct Obstruction

Strictures of the large bile ducts can be due to technical complications involving anastomoses, or other causes, including severe ischaemic and preservation injuries (see above) and chronic rejection with arteriopathy, among others.

Histopathology (Fig. 11.4) Post-transplant biliary complications histologically resemble the biliary disease of the native liver. Portal oedema and inflammation with neutrophilic granulocytes, resembling cholangitis, are common findings: the predominance of the neutrophilic infiltrate is very important in the differential diagnosis between post-OLT biliary complications and acute rejection. Cholestasis can be associated, while portal fibrosis and biliary cirrhosis represent the chronic evolution of this condition [12, 13].

11.3 Rejection

11.3.1 Acute Cellular Rejection

Acute cellular rejection (ACR) is defined as a predominantly lymphocytic inflammation of the graft due to an antigen mismatch between donor and recipient. The liver structures most commonly affected are the bile ducts and the vascular endothelia. Due to the high variability in onset and clinical symptoms, liver biopsy is mandatory in cases of suspect ACR.

Histopathology (Fig. 11.5) The main histological features of ACR are portal inflammatory infiltrate, endothelialitis and bile duct aggression. The inflammatory infiltrate characterizing ACR is mainly portal and with a prevalent lymphocytic component, although macrophages and both neutrophilic and eosinophilic granulocytes can be seen. The lymphocytes are CD8-positive and show the morphology of activated (or frankly blastic) T cells [14]. Lymphocyte-mediated bile duct injury is always present, with intraepithelial lymphocytes and associated bile duct regressive and reactive changes such as cytoplasmic eosinophilia and/or vacuolation, prominent nucleoli and occasional apoptosis [15]. Endothelialitis is defined as the presence of inflammatory cells in the subendothelial layer of the graft vascular (mainly venous) structures [16]. It is an important diagnostic feature in ACR, albeit not a specific finding since it can be detected in other pathological conditions (e.g. HCV recurrent hepatitis, infections) [17].

Differential Diagnosis Recurrent and *de novo* viral hepatitis (HCV, HBV, CMV, EBV), drug hepatitis, lymphoproliferative disorders and other disorders with a predominant inflammatory component. Clinical onset, serological and clinical data are mandatory for the differential diagnosis. The presence of a plasma cell component requires the differential diagnosis from plasmacellular HCV recurrent hepatitis or post-OLT autoimmune hepatitis: the role of plasma cells in acute rejection is still debated [18] (Fig. 11.6).

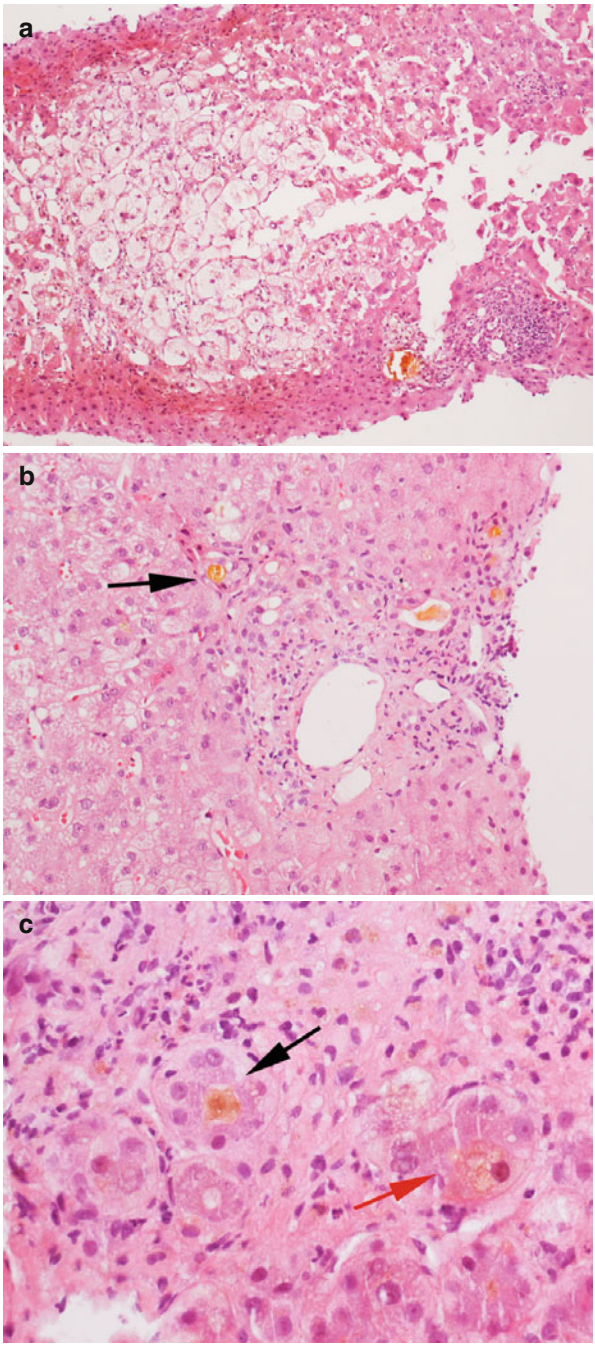

Fig. 11.4 A severe case of post-transplant biliary obstruction. (**a**) The lobule shows marked feathery degeneration of the hepatocytes and architectural distortion. (**b**, **c**) The portal tracts show inflammation with neutrophilic granulocytes, neoductulogenesis with bile plugs (*black arrows*) and intracellular cholestasis (*red arrow*). Magnification 10× (**a**); 20× (**b**); 40× (**c**)

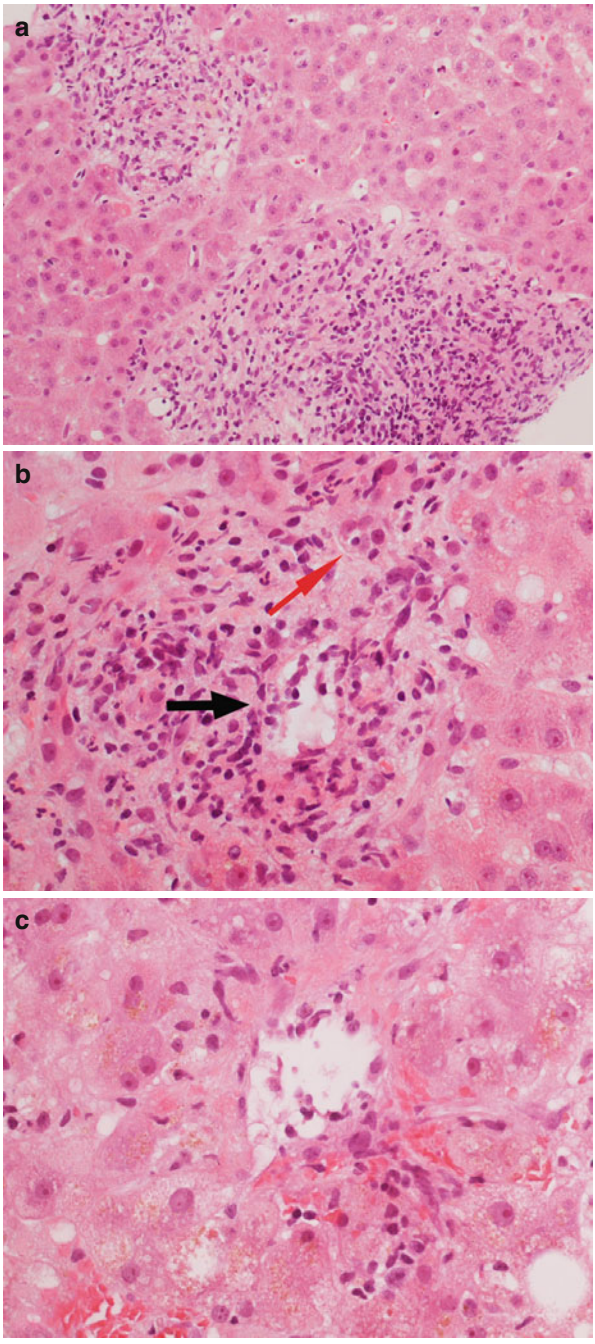

Fig. 11.5 (**a**) Acute cellular rejection (*ACR*) is characterized by a portal inflammatory infiltrate with portal expansion. (**b**) The inflammatory infiltrate is prevalently lymphocytic, although macrophages and granulocytes can be present. There is aggression of the vascular (*black arrow*) and biliary (*red arrow*) structures. (**c**) Endothelialitis is defined as the presence of inflammatory cells in the subendothelial layer of the graft vascular structures (in this case, a centrolobular vein). Magnification 20× (**a**); 40× (**b**, **c**)

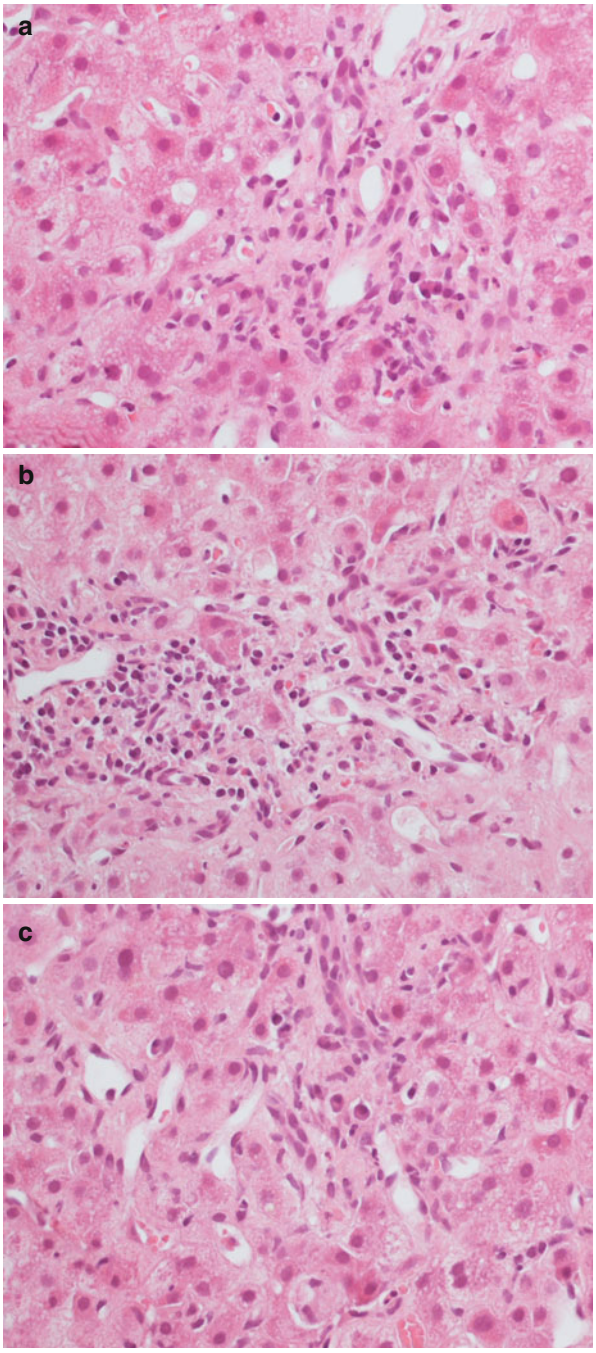

Fig. 11.6 A scarce (**a**) or more pronounced (**b**) plasma cell component, both in the portal tracts (**a**, **b**) and lobule (**c**) can be associated with rejection, recurrent viral hepatitis and *de novo* autoimmune hepatitis. The meaning of the plasma cell infiltrate after transplantation is controversial. Magnification 40×

Histopathological ACR is graded according to the 1997 Banff criteria as follows [14]:

Histopathological parameter	Description	Rejection activity index
Portal inflammation	Mild/focal	1
	Diffuse, mixed with occasional blasts and granulocytes	2
	Diffuse, mixed with numerous blasts and granulocytes, and interface activity	3
Bile duct involvement	Mild/focal inflammation	1
	Diffuse inflammation with epithelial injury to a few ducts	2
	Diffuse inflammation of most bile ducts; biliary cells necrosis	3
Endothelialitis	Presence of subendothelial lymphocytes in a minority of portal vessels	1
	Presence of subendothelial lymphocytes in most portal and centrolobular vessels	2

The absence of one or more criteria might lead to a diagnosis of indeterminate for rejection (Figs. 11.7 and 11.8), while according to these criteria a rejection activity index (RAI) of three to four represents mild ACR, a RAI of five to six moderate ACR, and a RAI greater than six severe ACR [14].

11.3.2 Acute Antibody-Mediated Rejection

Antibody-mediated rejection (AMR), also called humoral rejection, is defined as liver injury mediated by pre-existing or *de novo* antibodies against graft antigens. The graft antigens most commonly involved are AB0 and other endothelial surface molecules or (more rarely) MHC class I on the graft lymphocytes. AMR can manifest after hours, especially in AB0-incompatible transplants with pre-existing recipient antibodies, or days after reperfusion: the terms hyperacute and acute AMR are used depending on the timing and severity of graft dysfunction onset. At gross examination, the graft is swollen, oedematous and flaccid, often with visible thrombosis of the major hepatic vessels.

Histopathology (Fig. 11.9) AMR is primarily acute endothelial damage to virtually all liver vascular structures, which show fibrin deposition and granulocytic infiltrate. Accordingly, the main histopathological appearance is that of oedema and haemorrhage of the portal and periportal regions, with an inflammatory infiltrate predominantly composed of neutrophilic and eosinophilic granulocytes in the absence of lymphocytes. The most severe cases and all hyperacute cases present fibrin deposition in the sinusoids, portal and centrolobular veins, together with thrombosis. The lobular hepatocytes show necrosis and ballooning of variable degrees and extension [19].

As in the renal AMR, the antibody-antigen complexes activate the complement cascade, which mediates the endothelial damage. Accordingly, C4d positivity in the

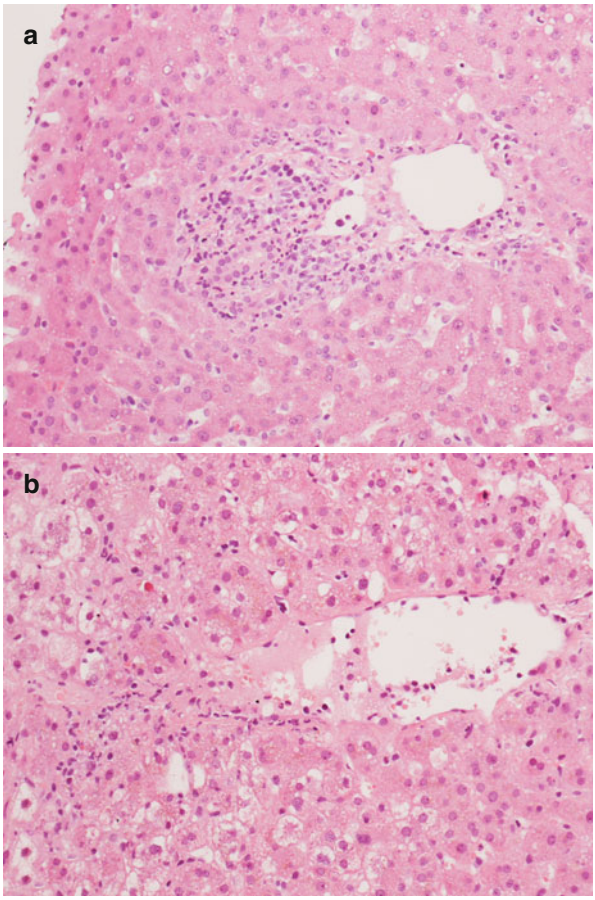

Fig. 11.7 A histological picture with only one or two criteria for rejection poses the diagnosis of indeterminate for rejection according to Banff. In these cases there can be (**a**) a mild portal infiltrate possibly with bile duct aggression or (**b**) mild and focal endothelial aggression of centrolobular veins. Magnification 20×

liver graft can also be detected by immunohistochemistry and immunofluorescence, while positivity in the portal tracts is considered of diagnostic help in cases of AMR. However, the usefulness of C4d is not as well established in the liver graft as it is in kidney transplantation [14, 20, 21] (Fig. 11.10).

11.3.3 Chronic Rejection

Chronic rejection is defined as a progressive loss of graft bile ducts commonly resistant to immunosuppression. Although its incidence is low, chronic rejection represents a major cause of graft loss and retransplantation in the long term. It is characterized by a progressive loss of the bile ducts, without a significant inflammatory infiltrate, and by a post-transplant arteriopathy of the large arteries.

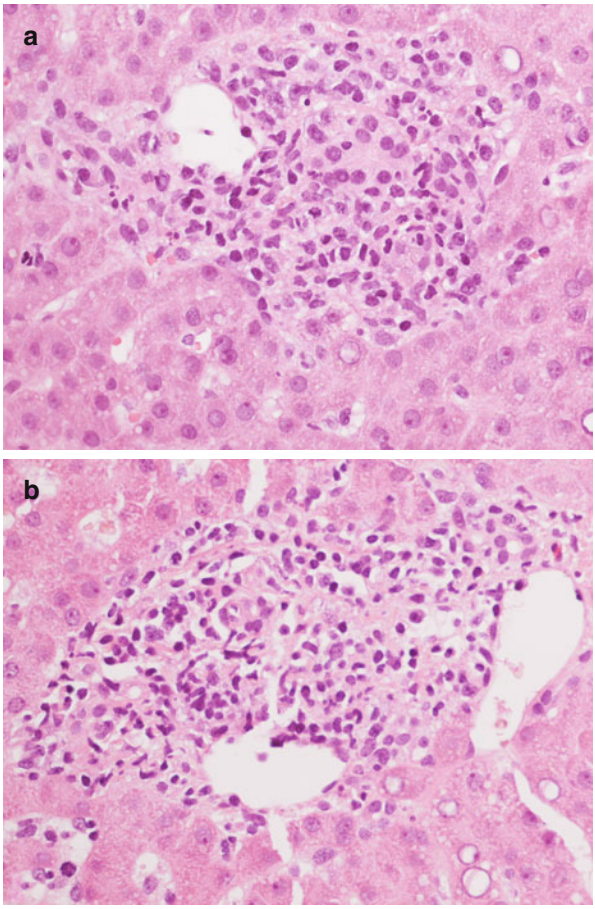

Fig. 11.8 (**a**, **b**) Detail on portal tract involvement in indeterminate for rejection, characterized by an inflammatory infiltrate, marked bile duct regression and focal subendothelial lymphocytes. Magnification 40×

Histopathology (Fig. 11.11) Although a lymphocytic bile duct infiltrate can be visible in the first phases of chronic rejection, the main histopathological feature is the loss of at least 50 % of the portal bile ducts, without direct inflammatory aggression and without ductular proliferation, possibly associated with "dysplastic-like" cell alterations [22]. Cholestasis is a common feature. Since bile duct loss is gradual, involving most of the portal tracts in the long term, it is even recommended that the graft biopsy contain no fewer than 20 portal tracts for a diagnosis of chronic rejection.

Graft arteriopathy represents another feature of chronic rejection: it begins with a subintimal infiltration by foam cells, activation of the endothelial cells and narrowing of the lumens. With time, a fibrotic obliteration of the hepatic arteries is visible, resulting in hepatocytic regression and necrosis of zone 3 [23].

Differential Diagnosis "Vanishing bile duct syndrome" and recurrent primary sclerosing cholangitis. Portal tract expansion is normally present in cholangitis,

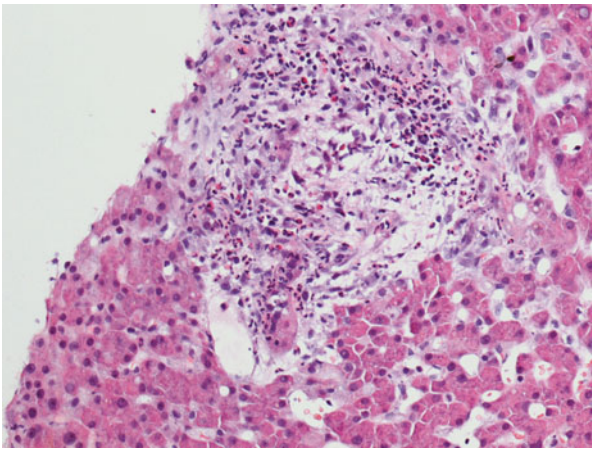

Fig. 11.9 Antibody-mediated rejection is histologically characterized by portal oedema and haemorrhage, with fibrin deposition and a neutrophilic and eosinophilic infiltrate, with endothelial damage. Magnification 20×

together with regressive changes in the biliary epithelium. Primary sclerosing cholangitis as the primitive disease, immunosuppression status and the timing of onset help in the differential diagnosis [9, 24].

11.4 Recurrence of Primitive Disease

11.4.1 Recurrent Hepatitis C

End-stage liver disease due to chronic hepatitis C (HCV) is the principal indication for OLT in the Western world. Reinfection after OLT is universal, and up to 70 % of graft recipients experience recurrent HCV.

Histopathology (Figs. 11.12 and 11.13) Recurrent HCV has recently been divided into three histopathological variants: the "usual" form (acute and chronic), fibrosing cholestatic HCV (FCH) and plasma cell-rich recurrent hepatitis [25, 26].

The "usual" acute recurrent HCV shows lobular damage, similar to acute HCV in the native liver, with lobular disarray, numerous Councilman bodies and spotty necrosis with Kupffer cell activation. When present, portal tract involvement is usually very mild. In the chronic phases, a portal lymphocytic infiltrate with interface activity becomes evident, and the lobular activity (Councilman bodies in particular) depends on direct viral replication in the chronic and acute phases. Recurrent HCV can sometimes overlap post-surgical damage or ACR hampering the diagnosis as some morphological features of recurrent HCV, such as endothelialitis and bile duct damage, mimic other graft diseases (Fig. 11.14). HCV RNA quantitation by means of RT-PCR should always be considered in HCV-positive recipients, as it has a good diagnostic and prognostic value in the early post-transplant phases [27–29].

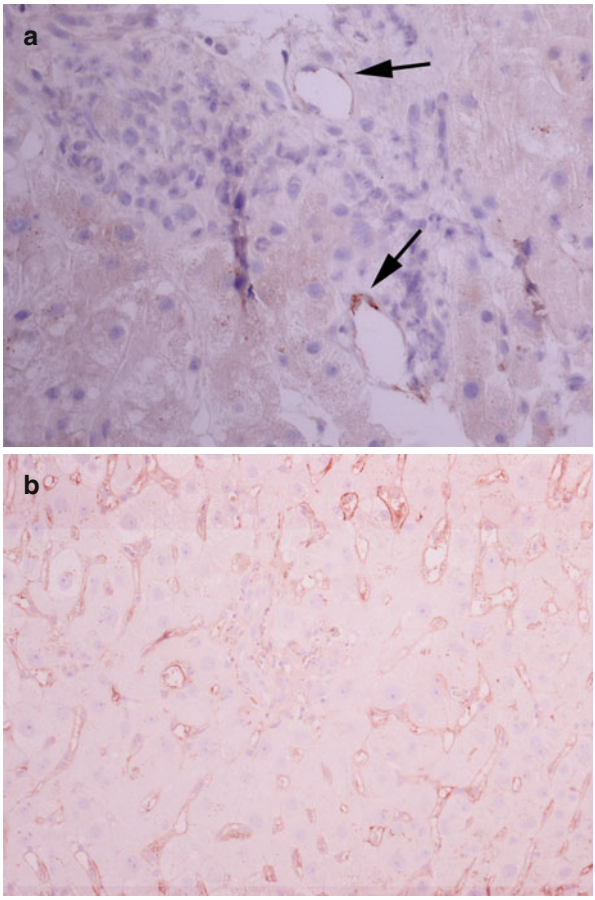

Fig. 11.10 (**a**) A case of antibody-mediated rejection (AMR) with specific immunohistochemical positivity for C4d in the endothelia (*arrows*): this kind of positivity is considered diagnostic for AMR (see *arrows*). (**b**) Another case with sinusoidal C4d positivity, considered not diagnostic for AMR. Magnification 40×

FCH is a peculiar highly aggressive presentation of recurrent HCV, characterized by early onset (within 1 year), rapid fibrosis progression and a poor response to antiviral therapies. Overimmunosuppressed recipients are at higher risk. At liver biopsy, FCH shows hepatocyte swelling and ballooning, spotty necrosis with Councilman bodies, cholestasis with ductular reaction and a scarce mixed portal infiltrate. Periportal fibrosis and cirrhosis are common in the late stages.

Plasma cell-rich recurrent HCV and other variants such as granulomatous recurrent HCV are rare and not well studied. Nevertheless, they should be known so as not to miss this differential diagnosis. They probably represent variants related to a "hyperimmune" status of the recipients or the immunosuppressive regimen (e.g. pegylated-interferon). As stated above, the role of plasma cells in recurrent HCV and acute rejection, and their meaning in possible de novo autoimmune damage, is still debated, making any differential diagnosis difficult (especially in overlap ACR-HCV recurrent hepatitis) [18].

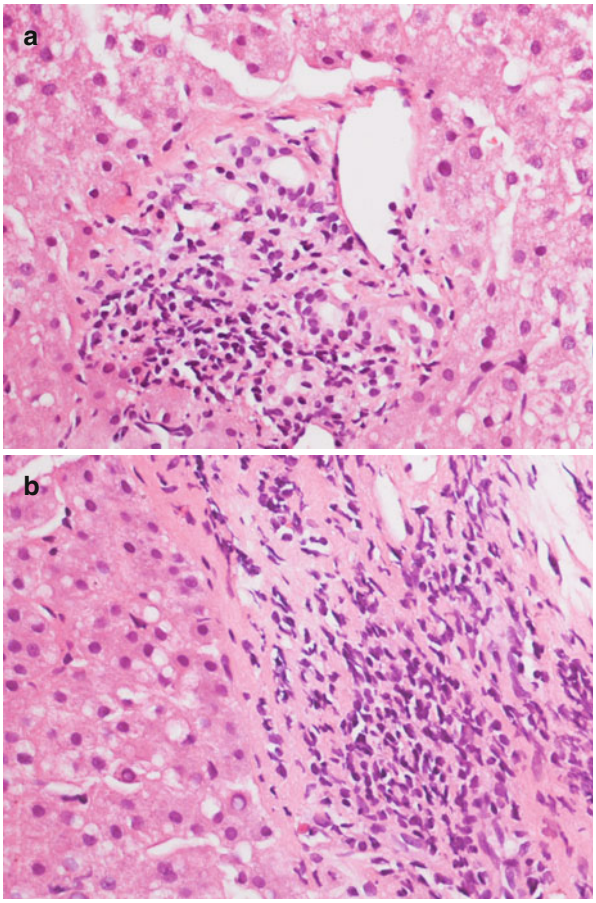

Fig. 11.11 (**a**) A case of chronic rejection with chronic portal inflammation but without direct aggression of the bile ducts, which show biliocyte regression. (**b**) In advanced cases there is loss of the biliary structures in at least 50 % of the portal bile ducts. Magnification 40×

11.4.2 Recurrent Hepatitis B

Compared to the last decades, the risk of a hepatitis B virus (HBV) re-infection after OLT has diminished due to advances in antiviral therapies and the possibility to transplant HBV-positive recipients with no dosable viraemia.

Histopathology Early HBV proliferation in the graft is visible with immunohistochemistry (anti-HBcAg antibody) also without appreciable histological modifications. Up to 6 months after OLT, lobular hepatitis is seen characterized by spotty necrosis, Kupffer cell activation and "ground-glass" appearance of the hepatocytes [30]. The overall picture resembles acute HBV in native livers, but antiviral therapy and immunosuppression can modify the histopathology [9]. Indeed, portal involvement is generally mild. In the late phases (>6 months), recurrent HBV becomes

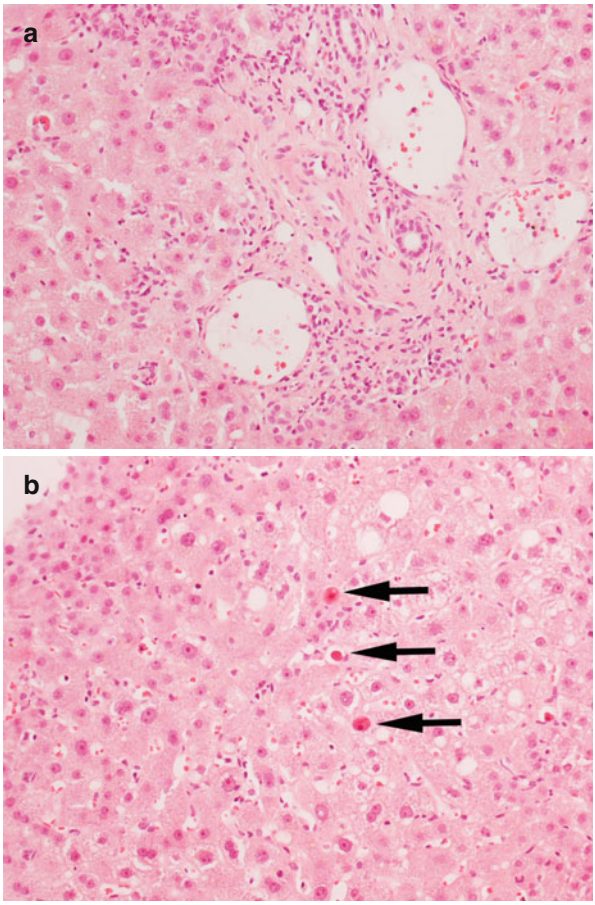

Fig. 11.12 Classic acute post-transplant recurrent HCV shows scarce portal inflammation (**a**), and a severe lobular necrosis with Councilman bodies (*arrows*) and hepatocytic polymorphism (**b**). Magnification 20×

chronic, and a lymphocytic portal inflammation with interface activity ("piecemeal necrosis") completes the picture. Although the response to antiviral therapy is generally good, fibrosis progression can lead to end-stage liver graft.

11.4.3 Recurrent Autoimmune Hepatitis and Biliary Diseases

Chronic conditions such as autoimmune hepatitis (AH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are minor causes of end-stage liver and OLT. However, the recurrence rates of these diseases in the graft are very high (up to 50 % according to some series). Generally, these diseases show the same histopathological features in primitive livers and recurrent forms.

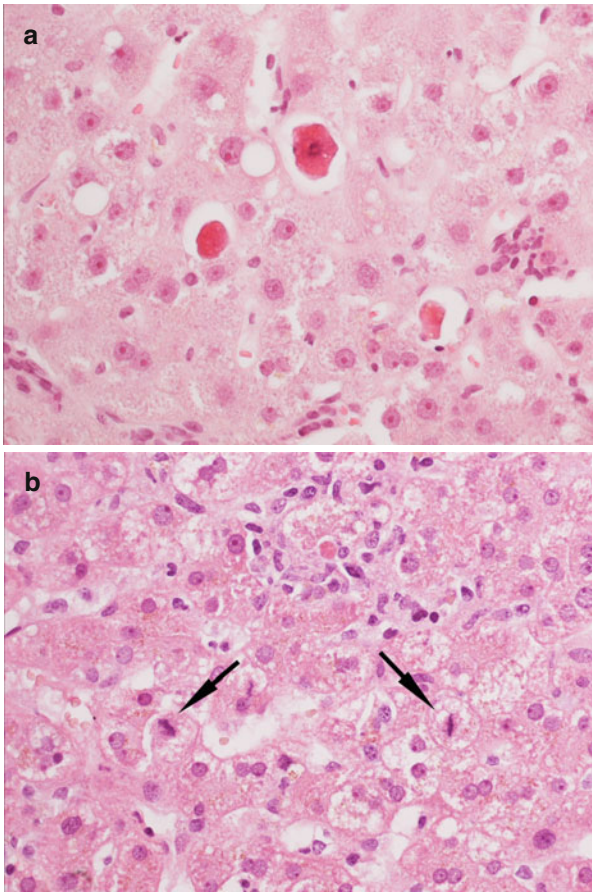

Fig. 11.13 A detail on acute lobular damage in recurrent HCV, characterized by several acidophilic Councilman bodies (**a**) and lobular regeneration (mitosis, *arrows*). Magnification 40×

Histopathology Like primitive AH, recurrent AH shows a prominent lymphocyte- and plasma cell-rich portal inflammation, with interface activity ("piecemeal necrosis") of moderate/severe degree [31]. The biliary structures are often spared. Mononuclear inflammatory cells, especially plasma cells, are often visible in the lobules and in the central veins, posing the differential diagnosis with rejection.

Recurrent PBC is characterized by a lymphocytic aggression of the bile ducts with occasional non-necrotizing epithelioid granulomas. These changes are diagnostic of recurrent PBC, but they are focal and often require a large biopsy with many portal tracts to be appreciable [32]. The lobules show spotty inflammation, intrahepatocellular cholestasis, Mallory bodies and sometimes copper deposition. Immunohistochemistry for Keratin 7 highlights ductular proliferation and hepatocytic ductular metaplasia. Serum autoantibody quantitation is required for a definite diagnosis.

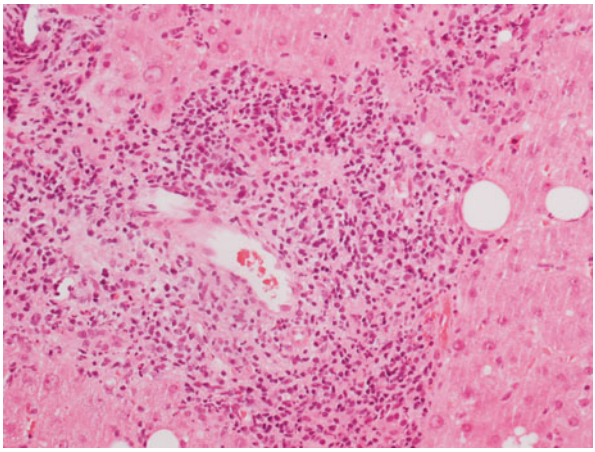

Fig. 11.14 Portal involvement in a case of overlapping acute cellular rejection and chronic recurrent HCV. A granulocytic infiltrate is seen together with the lymphocytic inflammatory infiltrate, with interface activity and subendothelial lymphocytes. Magnification 20×

The histopathological picture of recurrent PSC is characterized by bile duct loss and ductular proliferation, together with an infiltrate of neutrophilic granulocytes, with portal fibrosis and "onion-skin" fibrosis seen in the long term [24]. The lobules show the same changes as recurrent PBC. Biliary stenosis places the differential diagnosis with post-surgical bile duct obstruction: the timing of onset, the presence of "onion-skin" fibrosis and biliary non-anastomotic stenosis are useful for the diagnosis.

11.5 Allograft Infections

11.5.1 Cytomegalovirus

Cytomegalovirus (CMV) graft infection has an incidence from 17 to 29 % according to the different series, and overimmunosuppression is the principal risk factor.

Histopathology (Fig. 11.15) The diagnostic hallmark of CMV infection is represented by nuclear inclusions, typically eosinophilic with a clear halo, seen in virtually all graft cells, albeit endothelial cells are the most commonly affected. Sometimes these nuclear inclusions are associated with smaller basophilic cytoplasmic inclusions. Lobular spotty necrosis, centrolobular haemorrhage, mixed portal tract inflammatory infiltrate and (more rarely) microgranulomas and lobular microabscesses define the picture of CMV hepatitis [9, 12]. Apart from the nuclear inclusions, CMV graft infection does not show specific histopathological features and can sometimes overlap conditions such as rejection and other infections. In these cases, the immunohistochemistry with anti-CMV antibodies can be of use in the differential diagnosis.

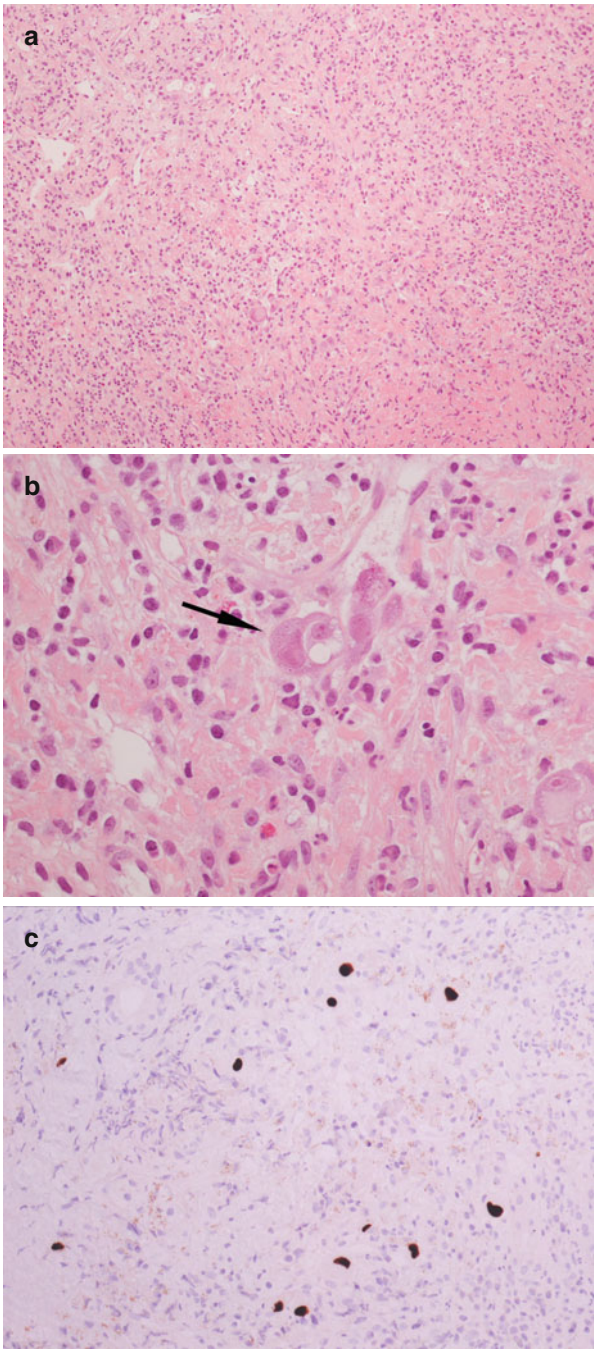

Fig. 11.15 (**a**) The overall histological picture of post-transplant CMV hepatitis is not specific, with lobular spotty necrosis, centrolobular haemorrhage, mixed portal and lobular inflammatory infiltrate; (**b**) nuclear eosinophilic inclusions with a clear halo are considered diagnostic. (**c**, **d**) Diagnostic confirmation comes from the immunohistochemical positivity for CMV in scattered cells. Magnification 10× (**a**); 20× (**c**); 40× (**b**, **d**)

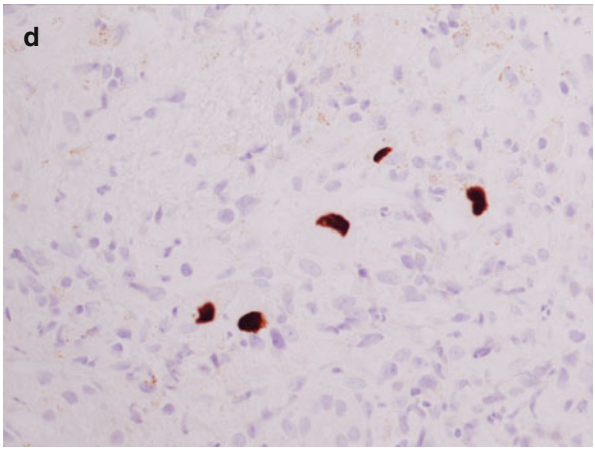

Fig. 11.15 (continued)

11.5.2 Epstein Barr Virus

The incidence of Epstein Barr virus (EBV) hepatitis after OLT is difficult to evaluate since it depends on donor and recipient EBV positivity before transplant, immunosuppression and viral replication in the graft [9]. Moreover, apart from post-transplant lymphoproliferative disease (PTLD), which represents the most severe EBV complication, the histological picture of the EBV graft damage is very variable and often masked by overlapping conditions.

Histopathology In the milder form, post-OLT EBV infection shows a mild portal and sinusoidal infiltrate of small lymphocytes, sometimes with slight nuclear atypia. A typical feature of EBV infection is the tendency of lymphocytes to line up within the sinusoids. A more severe form of EBV hepatitis is characterized by lobular spotty necrosis with Councilman bodies and mixed portal inflammatory infiltrate, containing large irregular lymphocytes and immunoblasts, and bile duct damage [33]. In situ hybridization for EBER is needed to confirm the diagnosis.

References

1. Fiorentino M, Vasuri F, Ravaioli M, Ridolfi L, Grigioni WF, Pinna AD, D'Errico-Grigioni A. Predictive value of frozen-section analysis in the histological assessment of steatosis before liver transplantation. Liver Transpl. 2009;15:1821–5.
2. Lo IJ, Lefkowitch JH, Feirt N, Alkofer B, Kin C, Samstein B, et al. Utility of liver allograft biopsy obtained at procurement. Liver Transpl. 2008;14:639–46.
3. Selzner M, Clavien PA. Fatty liver in liver transplantation and surgery. Semin Liver Dis. 2001;21:105–13.
4. Verran D, Kusyk T, Painter D, Fisher J, Koorey D, Strasser S, et al. Clinical experience gained from the use of 120 steatotic donor livers for orthotopic liver transplantation. Liver Transpl. 2003;9:500–5.

5. Kootstra G, Kievit J, Nederstigt A. Organ donors: heartbeating and non-heartbeating. World J Surg. 2002;26:181–4.
6. Selzner N, Rudiger H, Graf R, Clavien PA. Protective strategies against ischemic injury of the liver. Gastroenterology. 2003;125:917–36.
7. Kukan M, Haddad PS. Role of hepatocytes and bile duct cells in preservation-reperfusion injury of the liver grafts. Liver Transpl. 2001;7:381–400.
8. Kakizoe S, Yanaga K, Starzl TE, Demetris AJ. Evaluation of protocol before transplantation and after reperfusion biopsies from human orthotopic liver allografts: considerations of preservation and early immunological injury. Hepatology. 1990;11:932–41.
9. Adeyi O, Fischer SE, Guindi M. Liver allograft pathology: approach to interpretation of needle biopsies with clinicopathological correlation. J Clin Pathol. 2010;63:47–74.
10. Silva MA, Mirza DF, Murphy N, Richards DA, Reynolds GM, Wigmore SJ, Neil DA. Intrahepatic complement activation, sinusoidal endothelial injury, and lactic acidosis are associated with initial poor function of the liver after transplantation. Transplantation. 2008;85:718–25.
11. Demetris AJ, Kelly DM, Eghtesad B, Fontes P, Wallis Marsh J, Tom K, Tan HP, Shaw-Stiffel T, Boig L, Novelli P, Planinsic R, Fung JJ, Marcos A. Pathophysiologic observations and histopathologic recognition of the portal hyperperfusion or small-for-size syndrome. Am J Surg Pathol. 2006;30:986–93.
12. Odze R, Goldblum JR. Surgical pathology of the G.I. tract, liver, biliary tract, and pancreas. 2nd ed. Philadelphia: Elsevier; 2009.
13. Sanchez-Urdazpal L, Gores GJ, Ward EM, Maus TP, Buckel EG, Steers JL, Wiesner RH, Krom RA. Diagnostic features and clinical outcome of ischemic-type biliary complications after liver transplantation. Hepatology. 1993;17:605–9.
14. Aguilera I, Sousa JM, Gavilan F, et al. Complement component 4d immunostaining in liver allografts of patients with de novo immune hepatitis. Liver Transplant. 2011;17:779–88. Banff schema for grading liver allograft rejection: an international consensus document. Hepatology. 1997;25:658–63.
15. Scholz M, Auth MK, Markus BH. The immunological role of biliary epithelial cells in human liver transplant rejection. Transpl Immunol. 1997;5:142–51.
16. Ludwig J, Batts KP, Ploch M, Rakela J, Perkins JD, Wiesner RH. Endothelialitis in hepatic allografts. Mayo Clin Proc. 1989;64:545–54.
17. Yeh MM, Larson AM, Tung BY, Swanson PE, Upton MP. Endotheliitis in chronic viral hepatitis: a comparison with acute cellular rejection and non-alcoholic steatohepatitis. Am J Surg Pathol. 2006;30:727–33.
18. Demetris AJ, Sebagh M. Plasma cell hepatitis in liver allografts: variant of rejection or autoimmune hepatitis? Liver Transpl. 2008;14:750–5.
19. Demetris AJ, Jaffe R, Tsakis A, Ramsey G, Todo S, Belle S, Esquivel C, Shapiro R, Markus B, Mroczeck E, Van Thiel DH, Sysyn G, Gordon R, Makowka L, Starzl T. Antibody-mediated rejection of human orthotopic liver allografts. A study of liver transplantation across AB0 blood group barriers. Am J Pathol. 1988;132:489–502.
20. Haga H, Egawa H, Fujimoto Y, et al. acute humoral rejection and C4d immunostaining in AB0 blood type-incompatible liver transplantation. Liver Transpl. 2006;12:457–64.
21. Kozlowski T, Rubinas T, Nickeleit V, et al. Liver allograft antibody-mediated rejection with demonstration of sinusoidal C4d staining and circulating donor specific antibodies. Liver Transpl. 2011;17:357–68.
22. Hubscher SG. Transplantation pathology. Semin Liver Dis. 2009;29:74–90.
23. Nakazawa Y, Jonsson JR, Walker NI, et al. Fibrous obliterative lesions of veins contribute to progressive fibrosis in chronic liver allograft rejection. Hepatology. 2000;32:1240–7.
24. Demetris AJ. Distinguishing between recurrent primary sclerosing cholangitis and chronic rejection. Liver Transpl. 2006;12:S68–72.
25. Demetris AJ. Evolution of hepatitis C virus in liver allografts. Liver Transpl. 2009;15: S35–41.

26. Vasuri F, Malvi D, Gruppioni E, Grigioni WF, D'Errico-Grigioni A. Histopathological evaluation of recurrent hepatitis C after liver transplantation: a review. World J Gastroenterol. 2014;20:2810–24.
27. Gottschlich MJ, Aardema KL, Burd EM, Nakhleh RE, Brown KA, Abouljoud MS, Hirst K, Moonka DK. The use of hepatitis C viral RNA levels in liver tissue to distinguish rejection from recurrent hepatitis C. Liver Transpl. 2001;7:436–41.
28. D'Errico-Grigioni A, Fiorentino M, Vasuri F, Gruppioni E, Fabbrizio B, Zucchini N, Ballardini G, Morelli C, Pinna AD, Grigioni WF. Tissue hepatitis C virus RNA quantification and protein expression help identify early hepatitis C virus recurrence after liver transplantation. Liver Transpl. 2008;14:313–20.
29. Vasuri F, Morelli MC, Gruppioni E, Fiorentino M, Ercolani G, Cescon M, Pinna AD, Grigioni WF, D'Errico-Grigioni A. The meaning of tissue and serum HCV RNA quantitation in hepatitis C recurrence after liver transplantation: a retrospective study. Dig Liver Dis. 2013;45:505–9.
30. Thung SN. Histologic findings in recurrent HBV. Liver Transpl. 2006;12:S50–3.
31. Duclos-Vallee JC, Sebagh M, Rifai K, Johanet C, Ballott E, Guettier C, Karam V, Hurtova M, Feray C, Reynes M, Bismuth H, Samuel D. A 10 year follow up study of patients transplanted for autoimmune hepatitis: histological recurrence precedes clinical and biochemical recurrence. Gut. 2003;52:893–7.
32. Khettry U, Anand N, Faul PN, Lewis WD, Pomfret EA, Pomposelli J, Jenkins RL, Gordon FD. Liver transplantation from primary biliary cirrhosis: a long-term pathologic study. Liver Transpl. 2003;9:87–96.
33. Randawa PS, Markin RS, Starzl TE, Demetris AJ. Epstein-Barr virus-associated syndromes in immunosuppressed liver transplant recipient. Am J Surg Pathol. 1990;14:538–47.

Postoperative Technical Complications

12

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The technique of liver transplantation has been standardized to a considerable extent, at least in the majority of cases; however, this operation remains an exceptional surgical challenge. Numerous and life-threatening medical complications may appear in the early postoperative period, including "primary non-function," infectious disease, and immunological problems such as acute rejection.

Common surgical complications, namely, hemoperitoneum and/or perforation, may be similar in occurrence and treatment to other surgical procedures. We will focus on the most frequent postoperative technical complications which are related to the four different anastomoses performed during OLT. For this reason, we mainly recognize biliary and vascular complications.

12.1 Biliary Complications

The common bile duct is supplied through arteries coming from the gastroduodenal artery and running at the right and the left border of the bile duct which may have communication with the right or left hepatic artery which represents the remaining 30–40 % of bile duct arterial perfusion [1]. Due to this anatomical situation, it is advisable to avoid denudation of the graft's bile duct during the preparation for the anastomosis to preserve the arterial supply. Due to the vulnerability of arterial perfusion, the biliary epithelium is highly susceptible to ischemic injury, and severe hypotension or transient arterial thrombosis may frequently lead to ischemic cholangiopathy with biliary necrosis and cast formation [2]. In a recent survey of more

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than 17,000 liver transplantations performed in the United States, biliary complications requiring treatment within 6 months after OLT occurred in 15 % of cases, although only 3–4 % required surgical revision [3].

Biliary complications are usually divided in two main groups, depending on the site of the problem: anastomotic and non-anastomotic.

12.1.1 Anastomotic Complications

The most common risk factors for anastomotic complications are inappropriate surgical technique, arterial complications, and type of the graft (partial graft vs whole graft [1]. Other factors such as donor age and MELD score have been related to a higher incidence of biliary anastomotic complications [1, 4–6].

Higher incidences of biliary complications have been reported in the case of split liver and living donor liver transplantation [7, 8]. In the case of partial graft liver transplantation, the primary site is bile leaks from the resection surface; more common complications are due to the presence of anatomical variants, multiple and small hepatic ducts which should be reconstructed, and leaks from the caudate lobe [1, 7, 8].

Anastomotic biliary leakage is usually described at the point of T-tube insertion. Among 11,000 liver transplantations, it has been reported in 8.2 % of cases; however, a decrease to 4.9 % has been described in the most recent period [1, 4]. It is generally an early complication, within the first month after transplantation or at the time of T-tube removal [9]. It can be managed by leaving the T-tube open; when the problem persists, ERC is the treatment of choice, and sphincterotomy with or without a plastic stent is effective in almost 90 % of cases [10]. In cases of early leaks within 1–2 weeks, a large defect or suspected bile duct necrosis, primary surgical revision, and bilioenteric anastomosis might be required.

The percutaneous approach is rarely required except for leaks from a hepatojejunostomy. In a few cases, the presence of a subhepatic abscess may require percutaneous US- or CT-guided aspiration.

Anastomotic stenosis may be present in 10–15 % after liver transplantation [6]. Early anastomotic strictures are usually a surgical failure and require urgent surgical revision (most often a hepato-jejunostomy is advisable), while late strictures may be a consequence of ischemic damage, leaks, or other factors.

Anastomotic strictures are usually managed by ERC and eventually balloon dilatation [11]. Overall, 60–90 % of these complications can be treated endoscopically [11, 12]. In the case of prolonged biliary obstruction and cholangitis, surgical revision and bilioenteric anastomoses are necessary before allograft dysfunction appears [13].

In the case of stenosis of bilioenteric anastomoses, balloon dilatation is performed through a percutaneous approach (see Chap. 13).

Several technical modifications have been described, including end-to-end vs end-to-side or side-to-side anastomoses, and running vs interrupted sutures. However, randomized studies failed to show any statistical difference among different reconstruction techniques [14, 15].

Finally, as yet there is no general consensus on the benefit of the T-tube. The proposed advantages of reducing postoperative complications have not been confirmed by other recent studies [1, 16, 17]. A general consensus has been found on the use of the T-tube after DCD donation due to the high risk of biliary complications as reported by the ASTS guidelines [18].

12.1.2 Non-anastomotic Complications

The incidence of non-anastomotic strictures varies from 5 % up to 25 % [1]. Recently, there has been a slight increase due to the increased use of old donors, donors with extended criteria, and DCD [4].

The most frequent cause of non-anastomotic stenosis is the evolution of an early arterial thrombosis. Though immediate surgical revascularization may prevent biliary damage, due to the high susceptibility of the biliary epithelium to ischemic damage, late strictures may develop months after a primary complication; multiple stenosis and dilatation mimicking primary sclerosing cholangitis are the usual radiologic images (Fig. 12.1). Management is usually percutaneously (see Chap. 13); however, in up to two thirds of cases, progressive forms unresponsive to percutaneous treatment may require retransplantation.

Other causes can be ABO incompatibility, chronic rejection, and postoperative CMV infection [1, 19]. Furthermore, every effort should be made to reduce the

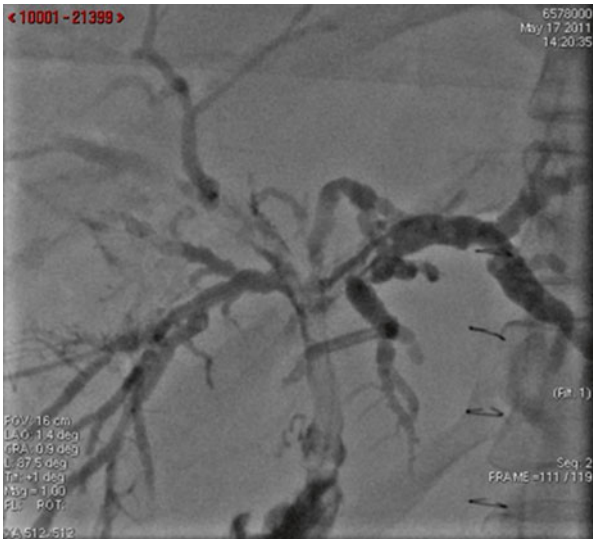

Fig. 12.1 Percutaneous transhepatic cholangiography showing typical findings of intrahepatic biliary dilatation and stenosis, "cast syndrome," due to posttransplant hepatic thrombosis. Early surgical revascularization was performed, but the patient required retransplantation 6 months later for recurrent episodes of cholangitis and septic complications

warm ischemia time, which is a well-established risk factor for this kind of complication, and to avoid cold ischemia time over 13 h [1, 20].

12.2 Vascular Complications

Postoperative vascular complications are related to caval, portal vein, or hepatic artery anastomoses.

12.2.1 Inferior Vena Cava Anastomoses

Liver transplantation with the preservation of the recipient inferior vena cava, the so-called "piggyback" technique described by Tzakis in 1989 [21], has been recently adopted in the majority of cases instead of the conventional technique, avoiding the dissection of the retrocaval space, the use of venovenous bypass, and reducing blood loss and renal impairment [22].

In spite of its advantages, this technique does not perfectly restore the physiological situation and may increase the risk of venous outflow stenosis or obstruction, which is the only drawback compared to the conventional caval anastomosis [23]. Cavo-caval side-to-side anastomosis and piggyback technique using the stump of the three major hepatic veins are the best-performing techniques to reduce/avoid postoperative complications [23, 24]. With these techniques, the incidence of complications might be around 1 %. The kinking or stricture of the anastomosis may cause an early Budd-Chiari syndrome or a chronic outflow obstruction. This latter may present with refractory ascites, jaundice, and alterations of coagulator factors with a normal liver and which are not justified by liver biopsy or presence of a liver disease. The diagnosis suspected by percutaneous ultrasound showing the absence of the physiological triphasic waves must be confirmed by cavography and measurement of pressure gradients (see also Chap. 13).

In the case of stenosis/kinking, the percutaneous approach with balloon dilatation and, if necessary, stent placement may solve the problem in almost 80 % of patients (see Chap. 13). In a few cases, a second infracaval termino-lateral cavo-cavostomy is required in order to solve the problem and save the organ [25]. When surgical or percutaneous approaches do not solve the problem or a Budd-Chiari syndrome develops, retransplantation can be required in nearly half the cases [23].

12.2.2 Portal Vein Anastomoses

Anastomotic stenosis of the portal vein is a rare complication after liver transplantation (occurring in 0.5–3 % of cases), but it is a potential cause of graft loss if not treated [26–28]; the majority of cases have been reported after living donor or split liver transplantation and in pediatric recipients. In these cases, alterations of biochemical liver function tests may be present, but the diagnosis must be

confirmed by Doppler ultrasound and portography. In the past, these complications were usually treated by surgical reconstruction of the anastomoses or retransplantation, while nowadays the percutaneous approach is the treatment of choice (see Chap. 13) [29].

Preoperative portal vein thrombosis in recipients is no longer considered a contraindication for OLT [30]. However, in these patients postoperative re-thrombosis may appear in up 10 % of patients [31]; postoperative prophylaxis using low-dose heparin has been suggested to reduce the incidence of re-thrombosis [31].

12.2.3 Hepatic Artery Anastomoses

These are probably the most complex anastomoses, since thrombosis of the hepatic artery is a life-threatening complication after OLT and an important cause of retransplantation and/or mortality. Early hepatic artery thrombosis is associated with bile duct necrosis followed by intrahepatic abscess and septic complications. In the case of late thrombosis, the presence of collaterals mainly derived from the phrenic arteries can prevent these dreaded complications [32]. A systematic review in 2009 showed that the median incidence of hepatic artery thrombosis was 4.4 %; it was higher among pediatric recipients and in low-volume transplant centers (less than 30 cases/year) [32]. The median time to detection was 6.9 days after surgery through Doppler ultrasound screening protocol performed daily or more frequently at least for the first week. In cases of suspected thrombosis, a CT scan or direct relaparotomy was performed. Revascularization can be successful in almost half of cases, but re-OLT is required in 50 % of cases [33]; mortality rates as high as 33 % have been reported. Several causes have been analyzed, but there is not agreement in all cases. There is a general consensus regarding the fact that the following are considered potential risk factors for postoperative occurrence of arterial thrombosis: presence of anatomical variants which may often require arterial reconstruction, donor age, retransplantation, and when the recipient's weight is significantly higher than the donor's weight [33–36]. In our experience, even the use of the infrarenal aortic conduit using an iliac cadaveric graft has a negative impact on hepatic artery patency [33, 37]. To avoid the use of an infra-aortic iliac conduit, alternative techniques such as arterial reconstruction on the splenic artery or microsurgery for end-to-end anastomoses with early administration of antiplatelet agents seem to reduce the incidence of this severe complication [36, 37].

It should be emphasized that intimal dissection of the artery due to a vigorous manipulation of the anastomotic sites, either of the donor or the recipient, can lead to intimal flap causing early thrombosis. For other situations such as ABO incompatibility, the use of reduced/split grafts, and cold ischemia time, no consensus has been found in the literature.

If arterial thrombosis is recognized early, surgical revascularization may be attempted with good long-term results and organ saving [38]. This technique may decrease the need for retransplantation. If revascularization fails or intrahepatic abscesses are present at the time of relaparotomy, retransplantation remains the only

chance of cure. This strategy tries to save the number of organs as much as possible due to their shortage.

Risk factors for late arterial thrombosis have been reported as low donor weight, previous surgery, and long operative time for transplantation. In these cases, the presence of collateralization from phrenic arteries may ensure satisfactory perfusion of the liver, saving the organ from retransplantation; ischemic cholangiopathy can be treated by interventional radiology (see also Chap. 13).

References

1. Seehofer D, Eurich D, Schlieker W, Neuhaus P. Biliary complications after liver transplantation: old problems and new challenges. Am J Transplant. 2013;13:253–65.
2. Deltene P, Valla DC. Ischemic cholangiopathy. Semin Liver Dis. 2008;28:235–46.
3. Axerold D, Lentine K, Xiao H, et al. National assessment of early biliary complications following liver transplantation: Incidence and Outcomes Liver Transpl. 2014;20:446–56.
4. Sundaram V, Jones DT, Shah NH, et al. Post-transplant biliary complications in the pre and post-model for end-stage liver disease era. Liver Transpl. 2011;17:428–35.
5. Serrano MT, Garcia G, Arenas J, et al. Outcome of liver transplantation using donors older than 60 years of age. Clin Transpl. 2010;24:543–9.
6. Karimiam N, Westerkamp A, Porte R. Biliary complications after orthotopic liver transplantation. Curr Opin Org Transplant. 2014;19:209–16.
7. Vagefi PA, Parekh J, Roberts JP, Freise CE. Outcomes with split liver transplantation in 106 recipients: the University of California experience from 1993 to 2010. Arch Surg. 2011;146:1052–9.
8. Lida T, Ogura Y, Olise F, et al. Surgery related morbidity in living donor liver transplantation. Transplantation. 2010;89:1276–82.
9. Thuluvath PJ, Pfau PR, Kimmey GB. Biliary complications after liver transplantation. The role of endoscopy. Endoscopy. 2005;37:857–63.
10. Akamatsu N, Sugawara Y, Hashimoto D. Biliary reconstruction, its complications and management of biliary complications after adult liver transplantation: a systematic review of the incidence, risk factors and outcome. Transpl Int. 2011;24:379–82.
11. Verdonk RC, Buis C, Porte RJ, et al. Anastomotic biliary strictures after liver transplantation. Causes and consequences. Liver Transpl. 2006;12:726–35.
12. Weber A, Prinz C, Gemgross C, et al. Long term outcome of endoscopic and/or percutaneous transhepatic therapy in patients with biliary stricture after orthotopic liver transplantation. J Gastroenterol. 2009;44:1195–202.
13. Sutcliffe R, Maguire D, Mroz A, et al. Bile duct strictures after adult liver transplantation: a role for biliary reconstructive surgery? Liver Transpl. 2004;10:928–34.
14. Davidson B, Rai R, Kurzawinski T, et al. Prospective randomized trial of end-to-end versus side-to-side biliary reconstruction after orthotopic liver transplantation. Br J Surg. 1999;86:447–52.
15. Castaldo ET, Pinson CW, Feurer ID, et al. Continuous versus interrupted suture for end-to-end biliary anastomosis during liver transplantation gives equal results. Liver Transpl. 2007;13:234–8.
16. Riedeger C, Muller M, Michalski C, et al. T-tube or no T-tube in the reconstruction of the biliary tract during orthotopic liver transplantation: systematic review and meta-analysis. Liver Transpl. 2010;16:705–17.
17. Lopez-Andjuar R, Oron E, Carregnato A, et al. T-tube or no T-tube in cadaveric orthotopic liver transplantation: the eternal dilemma. Ann Surg. 2013;00:1–9.
18. Reich DJ, Mulligan DC, Abt PL, ASTS standards on organ transplantation Committee, et al. ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation. Am J Transplant. 2009;9:2004–11.

19. Buis CI, Verdonk RC, Van der Jagt EJ, et al. Nonanastomotic biliary strictures after liver transplantation, part 1: radiological features and risk factors for early vs late preservation. Liver Transpl. 2007;13:708–18.
20. Heidenhain C, Pratschke J, Puhl C, et al. Incidence of and risk factors for ischemic-type biliary lesions following orthotopic liver transplantation. Transpl Int. 2010;23:14–22.
21. Tzakis A, Todo S, Starzl TE. Orthotopic liver transplantation with preservation of inferior vena cava. Ann Surg. 1989;210:649–52.
22. Jovine E, Mazziotti A, Grazi GL, et al. Piggy-back versus conventional technique in liver transplantation: report of a randomized trial. Transpl Int. 1997;10:109–12.
23. Cescon M, Grazi GL, Varotti G, et al. Venous outflow reconstructions with the piggy-back technique in liver transplantation: a single-center experience of 431 cases. Transpl Int. 2005;18:318–25.
24. Parrilla P, Sanchez-Bueno F, Figueras J, et al. Analysis of the complications of the piggy-back technique in 1112 liver transplants. Transplantation. 1999;67:1214.
25. Merenda R, Gerunda GE, Neri D, et al. Infrahepatic cavo-cavostomy as a rescue technique in complicated modified piggyback liver transplantation. J Am Coll Surg. 1997;185:576.
26. Godoy MA, Camunez F, Echenagusia A, et al. Percutaneous treatment of benign portal vein stenosis after liver transplantation. J Vasc Interv Radiol. 1996;7:273–6.
27. Lerut J, Tzakisn A, Bron K, et al. Complications of venous reconstruction in human orthotopic liver transplantation. Ann Surg. 1987;205:404–14.
28. Scantlebuty VP, Zajko AB, Esquivel CO, et al. Successful reconstruction of late portal stenosis after hepatic transplantation. Arch Surg. 1989;124:503–5.
29. Scantlebuty VP, Raby N, Karani J, Thomas S, et al. Stenoses of vascular anastomoses after hepatic transplantation: treatment with balloon angioplasty. Am J Roentgenol. 1991;157:167–71.
30. Ravaioli M, Zanello M, Grazi GL, et al. Portal vein thrombosis and liver transplantation. Evolution during 10 years of experience at the University of Bologna. Ann Surg. 2011;253: 378–87.
31. Rodriguez-Castro K, Porte R, Nadal E, et al. Management of nonneoplastic portal vein thrombosis in the setting of liver transplantation: a systematic review. Transplantation. 2012;94: 1145–53.
32. Bekker J, Ploem S, De Jong P. Early hepatic artery thrombosis after liver transplantation: a systematic review of the incidence, outcome and risk factors. Am J Transplant. 2009;9: 746–57.
33. Bekker, Mourad M, Liossis C, Gunson B, et al. Etiology and management of hepatic artery thrombosis after adult liver transplantation. Liver Transpl. 2014;20:713–23.
34. Grazi GL, Cescon M, Ravaioli M, et al. A revised consideration on the use of very aged donors for liver transplantation. Am J Transplant. 2001;1:67–9.
35. Cescon M, Zanello M, Grazi GL, et al. Impact of very advanced donor age on hepatic artery thrombosis after liver transplantation. Transplantation. 2011;92:439–45.
36. Yang Y, Zhao L, Ma Y, et al. Risk factors associated with early and late HAT after adult liver transplantation. World J Gastroenterol. 2014;14:10545–52.
37. Del Gaudio M, Grazi GL, Ercolani G, et al. Outcome of hepatic artery reconstruction in liver transplantation with an iliac arterial interposition graft. Clin Transplant. 2005;19:399–405.
38. Pinna AD, Craig S, Hiro F, et al. Urgent revascularization of liver allografts after early hepatic artery thrombosis. Transplantation. 1996;62:1584–7.

Percutaneous Treatment of Biliary and Vascular Complications

13

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Advances in surgical techniques and immunosuppression have made liver transplantation (LT) a first-line treatment for many patients with end-stage liver disease. The early imaging detection and the technological improvements in mini-invasive treatment of postoperative complications have contributed significantly to improved graft and patient survival, with interventional radiology playing a pivotal role in the multidisciplinary team following LT recipients.

13.1 Biliary Complications

After rejection, biliary complications are the most frequent sequelae after LT, mostly occurring within the first 6 months (10–30 % after LT from deceased donors and more than 36 % in living-donor liver transplant [LDLT]) resulting in mortality of 25–30 % [1]. However, their incidence in the adult population has been progressively decreasing over the years thanks to the surgical technique improvement and also as a result of early diagnosis and treatment that has significantly reduced the mortality associated with them. By contrast, in LDLT and in the pediatric population, they represent the most frequent cause of morbidity, with percentages of 30–60 % [1–3] in relation to the greater technical complexity in the reconstruction of the biliary tract.

The risk of specific biliary complications is related to the technique of biliary reconstruction: the incidence of complications is greater in the end-to-end

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choledochocholedocostomy (duct-to-duct technique) as compared to Roux-en-Y choledochojejunostomy [4]. In about 40 % of cases multiple separate duct anastomoses are necessary; in these cases, the most frequent complication is biliary stricture (described up to 68 % of cases), which may occur from several months to several years after LDLT.

Biliary complications can be divided into early (<3 months) and late (>3 months).

Early biliary complications are mainly represented by bile leakage (or biloma) that can be divided into intrahepatic non-anastomotic and anastomotic, biliary fistulas, and anastomotic stenosis.

Bile leakage is caused, in half the cases, by a biliary fistula at the site of the anastomosis – more frequently in end-to-end choledochocholedocostomy (2–25 %) – or from a fistula at the distal end of the Kehr T-tube, as a spontaneous event, or when it is removed (31 % of cases) [5–7]. Rarely, bile spillage may originate from the choledochojejunostomy, from the cystic duct stump of the graft or of the recipient, or from the sectioned surface of the liver in the case of dimensional reduction of the graft. The most frequent (30 %), but also less troubling, bile leaks develop in the *non-anastomotic extrahepatic site*, at the trans-choledochal crossing point of the Kehr T-tube. A trans-Kehr cholangiography shows a small linear collection along the course of the tube. In most cases, removal of the T-tube is sufficient, while in 35 % of cases surgical correction is needed. Sometimes it generates very large collections that are likely to get infected with abscess formation and/or biliary peritonitis; in these cases US-/CT-guided needle aspiration or percutaneous drainage is necessary, possibly associated with endoscopic papillotomy (EPT) in order to facilitate the bile outflow. *Anastomotic extrahepatic biliary leakages* often form large collections: they are caused by a surgical technical error in the anastomosis creation or by ischemic necrosis of the terminal portion of the graft common bile duct. Prognosis is significantly better in case of leakage of the end-to-end choledochocholedocostomy anastomosis rather than the choledochojejunostomy anastomosis, because they can be solved with endoscopic treatment or percutaneous transhepatic drainage, and rarely requires surgical correction (choledochojejunostomy). *Non-anastomotic intrahepatic biliary leakages* are severe early complications caused by ischemia and necrosis of the common bile duct (89 % of cases) due to stenosis or thrombosis of the main hepatic artery, or by vasculitis during hyperacute rejection, with or without associated biliary tract stenosis. Clinical symptoms include signs of sepsis, cholestasis, and intrahepatic multiple collections; the only possible treatment is re-transplantation.

Early biliary stenoses are frequently anastomotic, as consequence of an ischemic insult or a technical error in surgical suture. Clinically they may produce cholangitis and sepsis as a result of graft dysfunction.

Late biliary complications include anastomotic and non-anastomotic stenosis or obstruction (hilar or intrahepatic) and have a mean prevalence of 10 % (4–17 %) [8, 9]. They may be isolated, arising many months after LT, or be the consequence of recurrence or the evolution of an early complication, particularly ischemic.

Anastomotic biliary strictures are considered technical in nature, accentuated by fibrosis and scarring that may be secondary to, if not exacerbated by, graft ischemia:

they are usually single and short stenoses. *Non-anastomotic strictures* (hilar or intrahepatic) are the expression of a diffuse biliary insult with multifactorial etiology.

Non-anastomotic strictures are usually longer, extending from the hilum to the intrahepatic ducts; they seldom appear in isolated form, representing in this case the only sign of slow onset arterial thrombosis with well-developed collateral circulation; intraluminal mucous fragments and biliary sludge may worsen the obstruction.

The most frequent among biliary complications (6–29 %) [10, 11] is the early formation (few weeks after LT) of *fragments*, *stones*, *and biliary sludge* possibly without any biliary strictures, caused by acute rejection, ischemia, or infection. This could be favored by cyclosporine immunosuppressive treatment, inducing formation of cholesterol crystals: in the biliary tract, more frequently main bile ducts and common hepatic duct, bile is thickened, infected, or mixed with necrotic fragments. The clinical picture may vary from mild to severe forms characterized by the formation of large agglomerates in the biliary tract (casts): the "biliary cast syndrome" which has lower incidence (5–15 %) and usually is the result of an ischemic stenosis of the biliary tract.

Nonsurgical approach, either through percutaneous transhepatic cholangiography (PTC) or endoscopic retrograde cholangiopancreatography (ERCP), is almost always the first-line treatment, with well-established long-term results. In distal and mid common bile duct steno-obstruction, endoscopic procedures are usually preferred, as the risk of bleeding and septic complications is lower compared to percutaneous approach, which conversely is mandatory in biliary-digestive anastomosis and for treatment of proximal biliary complications (pre-anastomotic or intrahepatic sites). Moreover, the percutaneous approach has the advantage that it can always be performed in any clinical condition, lesion site, and type of biliary anastomosis. However, the choice between the two approaches is challenging and mainly depends on local experience.

The percutaneous approach involves the standard right lateral intercostal access for right biliary tracts or the subxiphoid access for left biliary tracts obtained by puncturing the corresponding segmental bile duct under fluoroscopic or ultrasound (US) guidance. A combined right midline transaxillary and subxiphoid percutaneous approach is employed for bilateral, intrahepatic bile accesses. After the biliary branch puncture, under fluoroscopy, contrast medium is injected to perform cholangiographic study to identify precisely leaks, stenosis, and endoluminal defects [12].

In case of biliary fistulas associated with leaks, after a preliminary PTC, percutaneous treatment includes the insertion of an internal–external biliary drainage catheter, placed across the fistula and left in situ until leak resolution (Fig. 13.1). The diversion of biliary flow should induce the complete resolution of small biliary fistulas, as reported in 62.5 % of cases within 2 months [13]. A higher success rate is reported for biliary leaks along the course of the Kehr T-tube after its removal. In case of large fistulas, removable covered stents can be placed across the biliary breach to allow healing.

In biliary steno-obstructions, after having crossed with a guidewire the stenotic bile duct, high-pressure angioplasty-type balloon catheter (bilioplasty) is inserted, chosen on the basis of the location of the stricture and the diameter of the normal bile duct (range from 6 to 12 mm). Usually, the balloon is inflated two or three

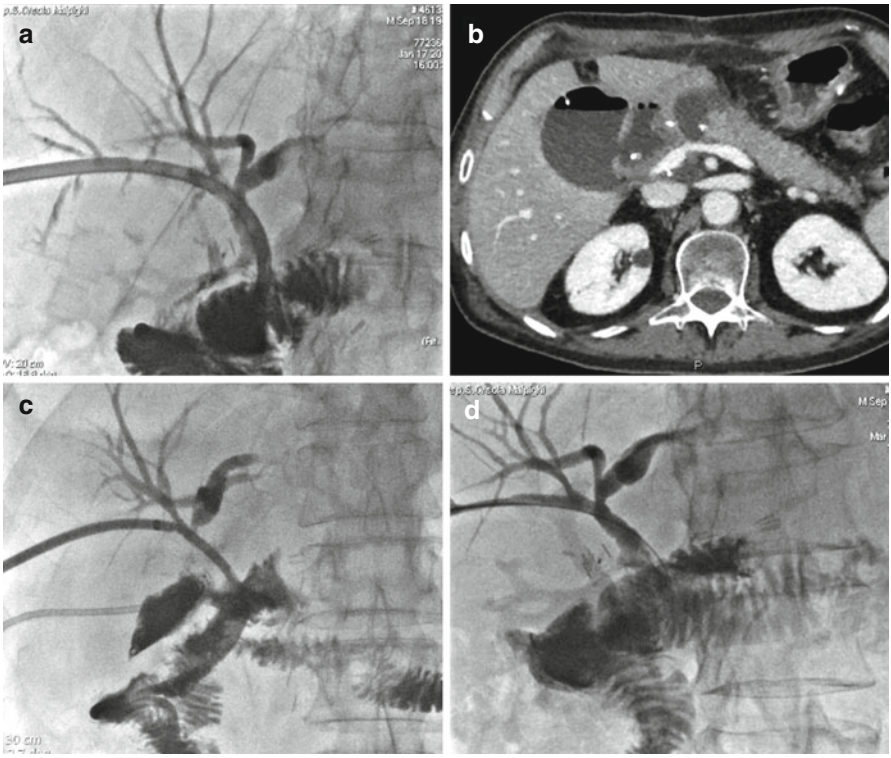

Fig. 13.1 (**a**) Cholangiogram shows a fistula at the site of the biliodigestive anastomosis, with an associated collection (biloma) as demonstrated on CT scan (**b**). The cholangiographic follow-up, performed 20 days after biliary drainage insertion and external drainage positioned under CT guidance into the biloma, shows reduction of the leakage (**c**). The cholangiographic follow-up at 40 days, after external drainage removal, shows resolution of the fistula, and therefore the biliary drainage was removed (**d**)

consecutive times at high pressure, for 1–3 min during the same session, and the success of dilation is defined as the disappearance of a balloon waist during inflation. After dilation, a transhepatic biliary drainage of adequate caliber is left in place across the stenosis, as a protection from restenosis during the healing process. The patient is then discharged and returns as an outpatient for follow-up cholangiography, repeated dilation, and to replace the biliary catheter at 2- to 3-week intervals. In most cases, more subsequent sessions of balloon dilations are required (mainly in anastomotic strictures) upsizing the balloon catheters, before the morphological and functional results become stabilized, while the biliary catheter has to remain in place for several weeks or months (Figs. 13.2 and 13.3). In the presence of complex strictures, multiple accesses may be required to place two or more catheters. The presence of sludge, stones, or bile casts upstream of the stenosis requires their removal through the use of occlusion catheters [8] or Dormia baskets, with immediate success in 60–90 % of cases.

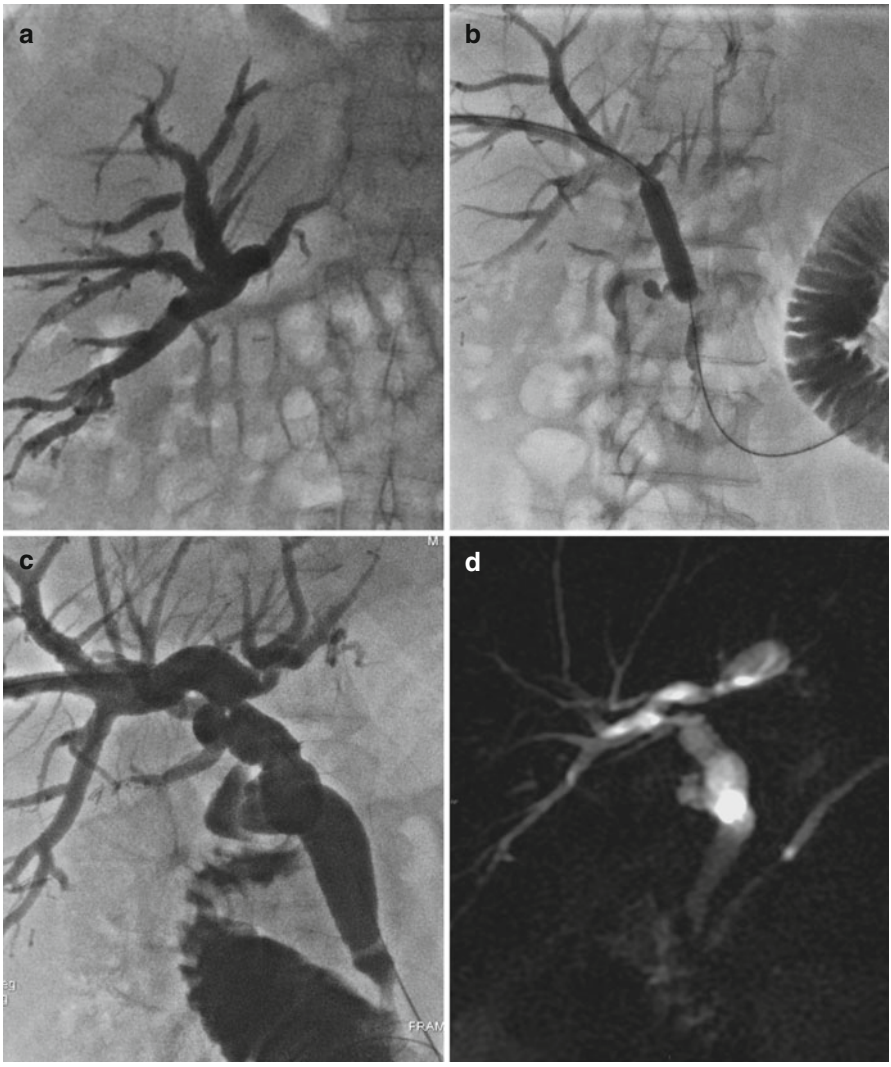

Fig. 13.2 (**a**) Percutaneous transhepatic cholangiography shows biliary stenosis at the site of the biliodigestive anastomosis. (**b**) The stricture was treated with balloon dilation. (**c**) Cholangiography performed after three bilioplasty sessions show complete resolution of the anastomotic stenosis. (**d**) Magnetic resonance cholangiogram 3 months after the completion of treatment confirms the stability of results

Among different variables in the percutaneous transhepatic balloon dilation protocols, none have proven to improve long-term patency. Success rate varies between 70 and 90 % at 3–6 years, with restenosis at 1 year in 20 % of cases [8, 13–15] depending on the technique. Nonischemic stenoses provide better results in less repeated sessions, whereas ischemic stenoses require a closer follow-up and multiple repeated bilioplasty sessions, but they obtain better secondary patency at 3 years [12].

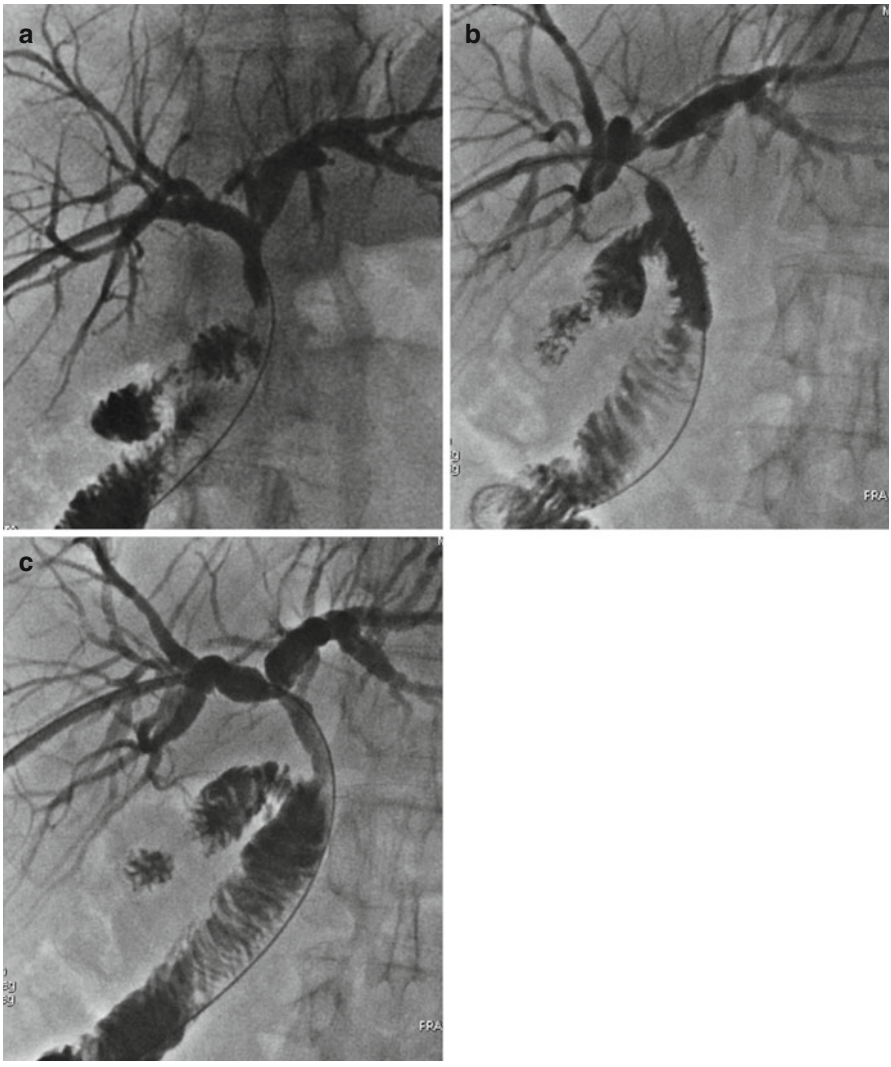

Fig. 13.3 (**a**) Percutaneous transhepatic cholangiography shows an almost complete obstruction at the site of the choledochocholedochal anastomosis associated with intrahepatic biliary duct dilatation. The patient was treated with repeated balloon dilation of the anastomotic stricture (**b**). At the end of the treatment, cholangiography shows restored patency of choledochocholedochal anastomosis (**c**)

In refractory biliary strictures with recurrence after balloon dilatation or surgical repair, it is possible to place self-expanding stainless steel stents, which exert a continuous outward radial pressure on the bile duct and prevent the elastic recoil of the wall. Stent positioning has a reported technical success rate approaching 100 % and 3-year patency rate of more than 90 % [16]. Placement of the recently introduced

covered removable stent across stenosis is an alternative option in cases of recurrence after repeated bilioplasty. The optimal removal period is about 6 months; after 9 months, removal becomes more difficult as it increases the risk of complications. Another possible complication is their migration due to lack of stability.

If the dilation causes hemobilia, a biliary drain should be left in place for a few days to prevent blood clots from creating a possible occlusion of the lumen.

Post-LT percutaneous procedures may incur in a series of complications (8–30 %) such as hemobilia, bleeding with subcapsular hematoma formation, cholangitis, pancreatitis, and fistulas due to biliary or duodenum perforation, usually spontaneously resolving [12, 16–18].

Sphincter of Oddi dysfunction, also termed ampullary dysfunction, occurs in 3–5 % of LT recipients and presents with cholestasis, dilatation of the distal bile duct, and cholangiography failing to detect any anatomic cause for biliary obstruction. It may be caused by operative denervation of the sphincter of Oddi during recipient hepatectomy, leading to subsequent impairment of ampullary relaxation and increased intraductal biliary pressure. The diagnosis may be confirmed clinically by decreasing cholestasis with T-tube unclamping, delayed drainage of contrast medium after cholangiography, and manometry [1]. Endoscopic sphincterotomy and biliary stenting are usually successful treatments, but conversion to a hepaticojejunostomy may occasionally be required.

13.2 Vascular Complications

Vascular complications after LT have a mean prevalence of 9 % and a wide variability among series (2–25 %), but are the most frequent cause of graft failure. They can be classified as early (within 3 months after LT, mostly including hemorrhages, thrombosis, or stenosis) or late (beyond 3 months, mainly comprising stenosis, thrombosis, and pseudoaneurysms) [19, 20]. The most frequent and critical vascular complications involve the hepatic artery and consist of hepatic artery stenosis and thrombosis, whereas portal and hepatic venous complications are less common and include stenosis and occlusion of the portal vein, hepatic veins, and inferior vena cava (IVC) [21–24]. In a series of 429 patients [21], arterial complications accounted for 6 % – including arterial thrombosis (58 %), stenosis (31 %), kinking (6 %), and pseudoaneurysms (5 %) – portal vein complications accounted for 1 %, and IVC and hepatic veins abnormalities for 2.5 %. In all cases, two therapeutic options, surgical or percutaneous, can be considered.

13.2.1 Arterial Complications

Hepatic artery thrombosis (HAT) is the most feared vascular complication, with incidence of 4–15 % in LT; its usual site is at the anastomotic level, with onset variable from weeks to months following LT, being more frequent during the early post-LT period [20]. Re-transplantation is required whenever thrombolysis and surgical thrombectomy do not allow salvage of the graft. Early HAT, appearing within

1 month after LT, more frequently needs a surgical approach of revascularization – if the graft function is still maintained – as an alternative of re-transplantation. Late HAT (after 1 month) can be treated more conservatively, by managing secondary ischemic complications such as biliary necrosis (treated with percutaneous biliary drainage) or parenchymal breakdown and abscess formation (treated with percutaneous abscess drainage). The significance of HAT stems from the relationship of the hepatic artery with the biliary epithelium; since the hepatic artery is the sole blood supply to bile ducts, its compromise can quickly lead to biliary ischemia, necrosis, bilomas, and biliary stricture onset.

The endovascular treatment of HAT should include intra-arterial thrombolysis (safely performed since 1–3 weeks after LT), currently achieved by combining mechanical thrombolysis (thrombus maceration) of the intra-arterial thrombus and pharmaceutical thrombolysis (infusion within the thrombus through a multiperforated catheter) by using urokinase or recombinant tissue plasminogen activator (r-tPA, Alteplase). In conjunction with intra-arterial thrombolysis perfusion, peripheral intravenous heparin is infused to prevent pericatheter thrombosis [25, 26]. Interval angiography after 12–24 h of thrombolysis is performed to assess the progress of the thrombolysis process and, if flow has been reestablished, assess for underlying anatomical defects such as arterial stenosis or kinking, to be treated consequently. Definitive success is defined as resolution of the thrombus without arterial anatomical defects reducing the arterial diameter lumen more than 50 % after 36–48 h of thrombolysis (Fig. 13.4). This treatment is burdened with bleeding complications, especially when performed in the early stages post-LT [27].

Hepatic artery stenosis (HAS) affects up to 11 % of transplant recipients and usually occurs at the anastomosis. The average onset of clinically significant stenosis is approximately 3 months and is more common in patients with a history of surgical clamp injury – responsible for proximal stenosis at the anastomotic site – and rejection, which commonly appears with multiple intrahepatic artery involvement [26]. Biliary sequelae can be observed in over 60 % of cases, with diffuse intrahepatic ducts involvement in up to 42 % [28]. Percutaneous endoluminal procedures are the first choice for HAS treatment, having less morbidity than surgery. HAS can be treated by percutaneous transluminal angioplasty (PTA), which must be performed at least 35 days after transplantation to prevent anastomotic lesions and bleeding [29]. This procedure, after intravenous administration of heparin, encompasses the selective catheterization of the involved artery, followed by the crossing of the stenotic segment with a guidewire on which an angioplasty double-lumen balloon catheter is advanced, placed over the stenosis, and inflated. Balloon size is determined by direct measurement of the patent portion of the hepatic artery at imaging (usually angio-CT). Possible complications of PTA (7–10 %) include hepatic artery rupture/perforation, thrombosis, dissection, and spasm [26, 30, 31]. Failure of the procedure is defined by relapse of stenosis, reported in 32–40 % of cases [26]. In case of recurrence, mainly due to longer segment stenosis (>3 cm) or after occurrence of parietal tears, a trans-stenotic metallic stent positioning is recommended [29] (Fig. 13.4).

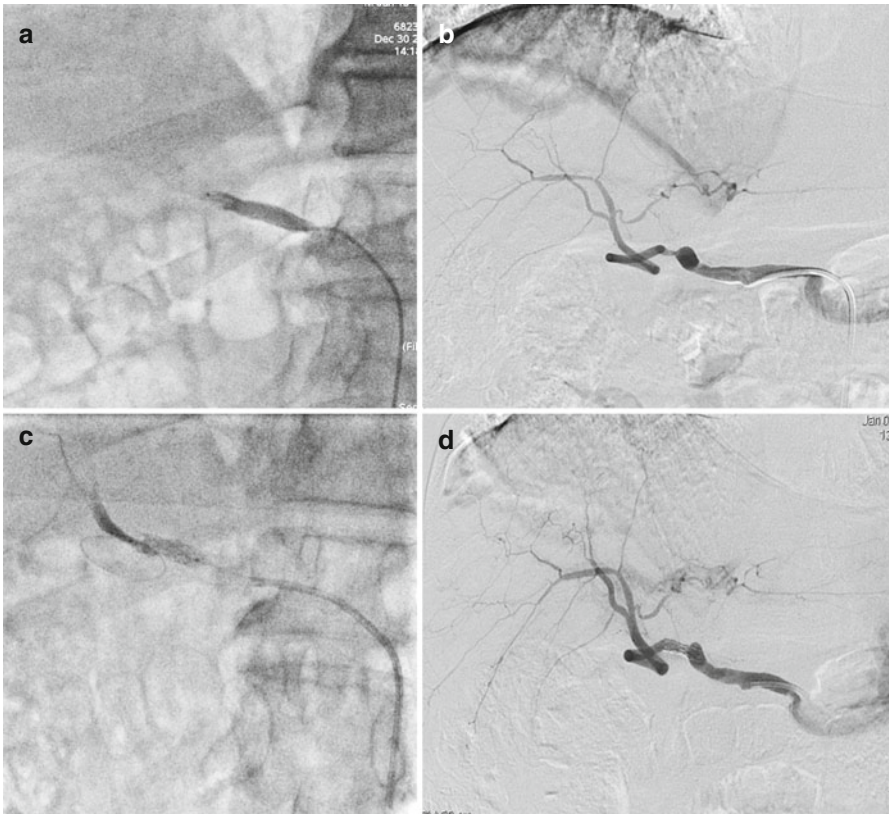

Fig. 13.4 (**a**) Selective hepatic arteriography shows complete thrombotic obstruction of the common hepatic artery at the surgical anastomosis with onset 3 months following LT; (**b**) the angiographic follow-up after 48 h from administration of urokinase showed resolution of the thrombus with residual stenosis, treated with deployment of a stent at the anastomotic level (**c**); final angiographic study demonstrates regular stent patency with preserved downstream arterial flow (**d**)

Pseudoaneurysm of the hepatic artery is a rare, but potentially catastrophic, complication of LT requiring prompt treatment. While most pseudoaneurysms are asymptomatic and discovered incidentally during surveillance imaging, rupture of the pseudoaneurysm may present with peritoneal signs, gastrointestinal hemorrhage, hemobilia, hypotension, or death. Extrahepatic pseudoaneurysms most commonly arise at the anastomosis and can be a sequela of PTA, while intrahepatic pseudoaneurysms may be secondary to infection, biopsy, or biliary interventions. Technological improvements of angiographic materials have led to fast, safe, and effective embolization procedures, which have replaced emergency surgery as the first treatment choice. Permanent materials including, plugs, metallic coils, or liquid materials (e.g., isobutyl cyanoacrylate [glue], polyvinyl alcohol [PVA]) serve to occlude proximal or distal vessels, and covered stent grafts are usually used for proximal large artery rupture and pseudoaneurysms. In pseudoaneurysms of the

hepatic artery, elective percutaneous treatment differs depending on its proximal or distal location: if the pseudoaneurysm occurs in the intrahepatic tract, endovascular embolization of the afferent branch of the aneurysm sac is performed by using micro-coils or permanent liquid embolic material. If the pseudoaneurysm is located in the extrahepatic tract, placement of a metallic covered stent graft is generally preferred to exclude the aneurysm sac from the main bloodstream.

Arterioportal fistula is a common transient phenomenon that can be detected in up to half of patients undergoing percutaneous biopsy. Most of these fistulas resolve spontaneously, with only approximately 10 % remaining past the first week after biopsy. A superselective embolization is the elective treatment by using appropriate angiographic material according to the fistula location [29, 31, 32].

Hepatic arterial kinking occurs in about 0.4 % of LT, and 7 % of HAS are associated to arterial kinking. The causes are due to donor or graft arterial redundancy or, more rarely, to external compression from surgical drainages. Surgical repair is the first choice, and, whenever not feasible, endoluminal correction can be attempted by stent positioning in order to straighten the vessel segment.

Splenic artery steal syndrome (*SASS*) is another rare (3–8 %) vascular complication frequently underdiagnosed: it is clinically comparable to HAS and the graft results underperfused due to flow diversion toward the splenic artery in the absence of an organic stenosis [33–35]. This syndrome is caused by splenomegaly with hypersplenism in the pre-LT period: after LT, portal hyperperfusion can stimulate hepatic arterial vasoconstriction, further predisposing to acute HAT. The diagnosis of SASS relies on the finding of a splenic artery >4 mm or 150 % larger than the hepatic artery. On angiogram, the hepatic artery shows reduced distal perfusion with a dominant flow into the splenic artery. The first-line treatment is surgical, with splenectomy or splenic artery ligation (banding), but an endovascular percutaneous approach can be also considered with partial splenic embolization (no more than 30 % of splenic parenchyma at each session).

Splenic artery aneurysms are more common in patients with cirrhosis and portal hypertension (0.7–2 %) [27, 36] due to high flow in the splenic artery: aneurysms >1.5 cm have a greater risk of rupture after LT caused by reduction of portal pressures and increased splenic arterial flow with growing artery caliber [36]. Therefore, it is mandatory to schedule a percutaneous treatment in a pre-transplant phase (endovascular embolization) or to plan a surgical ligation/splenectomy at the time of transplantation, to prevent any subsequent rupture.

13.2.2 Portal Vein Complications

Portal vein percutaneous interventions in LT include the management of several disease entities consisting of portal vein stenosis/thrombosis and recurrent liver cirrhosis with portal hypertension with and without varices. The procedures performed include portal vein angioplasty or thrombolysis with or without stent placement for portal vein thrombosis, transjugular intrahepatic portosystemic shunts (TIPS), or splenic embolization for cirrhosis.

Portal vein complications (1–13 %) are commonly due to excessive portal vein length, hypercoagulability, history of previous thrombus or portal manipulation, and caliber discrepancies between the donor and recipient veins.

Portal vein thrombosis is rare (approximately 3 % of LT) and can be treated, similarly to HAT, with pharmacologic thrombolysis followed by mechanical thrombectomy, especially when thrombosis is not recent. This technique is performed with dedicated angiographic equipment (catheters for thrombectomy) and followed by positioning of a metallic stent in the treated area, if there is mural thrombus.

In the rare (5 % of LT) *portal vein stenosis* (PVS), PTA is employed. This procedure is currently performed through a percutaneous transhepatic intercostal puncture of the right portal vein or more rarely through a transjugular intrahepatic approach [30]; in patients with severe coagulopathy (and increased risk of bleeding), or with abundant ascites, a transjugular ultrasound-guided approach is preferable [37]. Self-expanding bare stent placement may be indicated if recurrent (after many dilation sessions) stenosis occurs, although this precludes future re-transplantation.

13.2.3 IVC and Hepatic Vein Complications

Complications of the IVC and hepatic veins encompass stenosis and thrombosis and affect 1–2 % of liver transplant recipients in traditional anastomosis and up to 5 % in the "piggyback" technique, being more frequent in LDLT and pediatric LT, mainly due to higher rates of anastomotic torsion and kinking [38]. Narrowing of the IVC anastomosis may be due to surgical technique, hypercoagulability, or compression from graft edema or an adjacent fluid collection. Diagnostic confirmation of hemodynamically significant stenosis can be obtained at direct venography when a trans-stenotic gradient of more than 5 mmHg is measured [14]. Symptoms differ according to the degree of venous stenosis and range from asymptomatic to lower extremity edema, renal abnormalities, and Budd–Chiari syndrome ("outlet syndrome").

In *caval anastomotic stenosis*, percutaneous balloon dilatation via the jugular or femoral vein approach is often successful when there is a conventional anastomosis. Large-caliber balloon catheters are frequently used or, alternatively, smaller catheters positioned side-by-side and simultaneously inflated at high pressures ("kissing balloons" technique), with an immediate success rate of 80 %. As well as PVS, when there is narrowing recurrence or PTA-resistant stenosis, placement of a metallic stent is indicated, being aware that it precludes re-transplantation. In juxta-anastomotic stenosis of the hepatic veins, the treatment of choice is PTA along with a bare stent insertion [14, 32, 38–40].

Torsion of the "piggyback" anastomosis can induce a functional outflow syndrome without a significant trans-stenotic gradient. Torsion can be treated by deploying a metallic stent in the hepatic vein outlet, in order to prevent further kinking [32] (Fig. 13.5). PTA has worse results not destined to last over time: the reported 6, 12, and 60 months' primary patency rates are of 60–65 % [40]. The treatment of choice is surgery, with the conversion into a conventional end-to-side anastomosis.

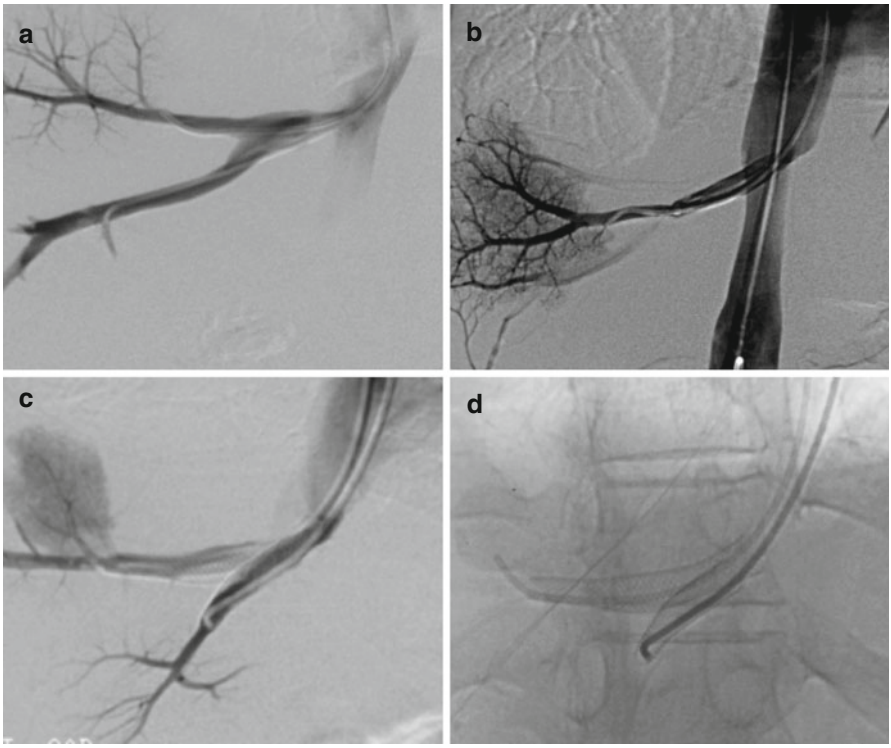

Fig. 13.5 In a functional outflow syndrome caused by torsion of the "piggyback" anastomosis, selective venography shows stenosis of the *right* (**a**) and *middle* (**b**) hepatic vein at the anastomotic site, confirmed by a trans-stenotic gradient of 8 mmHg. Two metallic stents were deployed across each hepatic vein and confluence into the inferior vena cava (**c**, **d**), achieving an improvement in the stenosis degree and a better flow confirmed by reduction of the trans-stenotic gradient (3 mmHg)

References

1. Wojcicki M, Milkiewicz P, Silva M. Biliary tract complications after liver transplantation: a review. Dig Surg. 2008;25:245–57.
2. Icoz G, Kilic M, Zeytunlu M, et al. Biliary reconstructions and complications encountered in 50 consecutive right lobe living donor liver transplantations. Liver Transpl. 2003;9:575–80.
3. Gondolesi GE, Varotti G, Florman SS, et al. Biliary complications in 96 consecutive right lobe living donor transplant recipients. Transplantation. 2004;77:1842–8.
4. Moser MAJ, Wall WJ. Management of biliary problems after liver transplantation. Liver Transpl. 2001;7:S46–52.
5. Kochhar G, Parungao JM, Hanouneh IA, et al. Biliary complications following liver transplantation. World J Gastroenterol. 2013;19:2841–6.
6. Londoño MC, Balderramo D, Cárdenas A. Management of biliary complications after orthotopic liver transplantation: the role of endoscopy. World J Gastroenterol. 2008;14:493–7.
7. Scanga AE, Kowdley KV. Management of biliary complications following orthotopic liver transplantation. Curr Gastroenterol Rep. 2007;9:31–8.

8. Righi D, Cesarani F, Muraro E, et al. Role of interventional radiology in the treatment of biliary strictures following orthotopic liver transplantation). Cardiovasc Intervent Radiol. 2002;25:30–5.
9. Alexopoulos SP, Henningsen JA, Jeffrey RB, et al. Management of biliary strictures following liver transplantation. Dig Dis Sci. 2009;54:25–7.
10. Barton P, Steininger R, Maier A, et al. Biliary sludge after liver transplantation: treatment with interventional techniques versus surgery and/or chemolysis. AJR Am J Roentgenol. 1999;164:865–9.
11. Sheng R, Ramirez CB, Zajko AB, et al. Biliary stones and sludge in liver transplant patients: a 13-year experience. Radiology. 1996;198:243–7.
12. Giampalma E, Renzulli M, Mosconi C, et al. Outcome of post-liver transplant ischemic and non-ischemic stenoses treated with percutaneous interventions: the Bologna experience. Liver Transplant. 2012;18:177–87.
13. Civelli EM, Meroni R, Cozzi G, et al. The role of interventional radiology in biliary complications after orthotopic liver transplantation: a single-center experience. Eur Radiol. 2004;14:579–82.
14. Zajko AB, Sheng R, Zetti GM, et al. Transhepatic balloon dilation of biliary strictures in liver transplant patients: a 10-year experience. J Vasc Interv Radiol. 1995;6:79–83.
15. Roumilhac D, Poyet G, Sergent G, et al. Long-term results of percutaneous management for anastomotic biliary stricture after orthotopic liver transplantation. Liver Transpl. 2003;9:394–400.
16. Gwon D, Shim HJ, Kwak BK. Retrievable biliary stent graft in the treatment of benign biliary strictures. J Vasc Interv Radiol. 2009;19:1328–35.
17. Glas L, Courbiere M, Ficarelli S, et al. Long-term outcome of percutaneous transhepatic therapy for benign bilioenteric anastomotic strictures. J Vasc Interv Radiol. 2008;19:1336–43.
18. Saad WE, Davies MG, Saad NE, et al. Transhepatic dilation of anastomotic biliary strictures in liver transplant recipients with use of a combined cutting and conventional balloon protocol: technical safety and efficacy. J Vasc Interv Radiol. 2006;17:837–43.
19. Itri JN, Heller MT, Tublin ME. Hepatic transplantation: postoperative complications. Abdom Imaging. 2013;38:1300–33.
20. Urbani L, Catalano G, Biancofiore G, et al. Surgical complications after liver transplantation. Minerva Chir. 2003;58:675–92.
21. Cavallari A, Vivarelli M, Bellusci R, et al. Treatment of vascular complications following liver transplantation: multidisciplinary approach. Hepatogastroenterology. 2001;48:179–83.
22. Zhao JC, Lu SC, Yan LN, et al. Incidence and treatment of hepatic artery complications after orthotopic liver transplantation. World J Gastroenterol. 2003;9:2853–5.
23. Boraschi P, Donati F. Complications of orthotopic liver transplantation: imaging findings. Abdom Imaging. 2004;2:189–202.
24. Quiroga S, Sebastià MC, Margarit C, et al. Complications of orthotopic liver transplantation: spectrum of findings with helical CT. Radiographics. 2001;21:1085–102.
25. Bhattacharjya T, Olliff SP, Bhattacharjya S, et al. Percutaneous portal vein thrombolysis and endovascular stent for management of post-transplant portal venous conduit thrombosis. Transplantation. 2000;69:2195–7.
26. Saad WE. Management of hepatic artery steno-occlusive complications after liver transplantation. Tech Vasc Interv Radiol. 2007;10:207–20.
27. Orons PD, Zajko AB. Angiography and interventional procedures in liver transplantation. Radiol Clin North Am. 1995;33:541–58.
28. Orons PD, Sheng R, Zajko AB. Hepatic artery stenosis in liver transplant recipients: prevalence and cholangiographic appearance of associated biliary complication. AJR Am J Roentgenol. 1995;165:1145–9.
29. Miraglia R, Maruzzelli L, Caruso S, et al. Interventional radiology procedures in adult patients who underwent liver transplantation. World J Gastroenterol. 2009;15:684–93.
30. Hamby BA, De R, Ge L, et al. Endovascular treatment of hepatic artery stenosis after liver transplantation. J Vasc Surg. 2013;57:1067–672.

31. Vignali C, Bargellini I, Cioni R, et al. Diagnosis and treatment of hepatic artery stenosis after orthotopic liver transplantation. Transplant Proc. 2004;36:2771–3.
32. Yamagiwa K, Yokoi H, Isaji S, et al. Intrahepatic hepatic vein stenosis after living-related liver transplantation treated by insertion of an expandable metallic stent. Am J Transplant. 2004;4:1006–9.
33. Sanyal R, Shah SN. Role of imaging in the management of splenic artery steal syndrome. J Ultrasound Med. 2009;28:471–7.
34. Farges O, Belghiti J. Editorial on "diagnosis and treatment of arterial steal syndromes in liver transplantation recipients". Liver Transpl. 2003;9:603–4.
35. Nussler NC, Settmacher U, Haase R, et al. Diagnosis and treatment of arterial steal syndromes in liver transplant recipients. Liver Transpl. 2003;9:596–602.
36. Robertson AJ, Rela M, Karani J, et al. Splenic artery aneurysm and orthotopic liver transplantation. Transpl Int. 1999;12:68–70.
37. Saad WEA. Portal interventions in liver transplant recipients. Semin Interv Radiol. 2012;29:99–104.
38. Ko GY, Sung KB, Yoon HK, et al. Endovascular treatment of hepatic venous outflow obstruction after living-donor liver transplantation. J Vasc Interv Radiol. 2002;13:591–9.
39. Weeks SM, Gerber DA, Jaques PF, et al. Primary Gianturco stent placement for inferior vena cava abnormalities following liver transplantation. J Vasc Interv Radiol. 2000;11:177–87.
40. Kubo T, Shibata T, Itoh K, et al. Outcome of percutaneous transhepatic venoplasty for hepatic venous outflow obstruction after living donor liver transplantation. Radiology. 2006;239:285–90.

Retransplantation (Causes, Outcome)

14

Valentina Rosa Bertuzzo, Giorgio Ercolani, Matteo Cescon, and Antonio Daniele Pinna

Orthotopic liver transplantation (OLT) has been established as the definitive therapy for all types of end-stage liver failure. In spite of the steady improvement in survival of OLT recipients over the past two decades, a proportion of those patients experience graft failure and require retransplantation (re-OLT). Over the last 10 years, the reported waitlist admission for re-OLT varied between 5.5 and 14 % [1–3].

Re-OLT indications can be divided into "early" and "late" causes.

Causes of early graft failure are:

- Primary non-function (PNF)
- Vascular complications (hepatic artery thrombosis, portal thrombosis, hepatic vein thrombosis)
- Acute rejection

Causes of late graft failure include:

- Recurrence of liver disease (viral infection, autoimmune diseases)
- Chronic rejection

Re-OLT is considered a high-risk procedure because of the technical demands of the operation and, in particular, the illness severity in the recipient. Even if good long-term survival rates have been reported in selected groups of patients [4, 5], re-OLT remains controversial because of inferior outcomes compared with primary OLT, especially considering the shortage of donated organs; in fact, the 5-year

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patient survival rates reported after re-OLT range between 36 and 52 % [3]. The leading causes of death after re-OLT were sepsis, peritonitis, and pneumonia [6, 7]. Furthermore, although there are no concerns regarding the use of a liver graft for re-OLT in emergency situations (such as PNF or vascular complications), some authors consider elective re-OLT, in particular for hepatitis C virus (HCV) recurrence, as a controversial procedure.

In order to recognize which patients could benefit from a re-OLT, many authors analyzed the variables associated with graft failure after re-OLT; recent studies reported the following factors as the main independent predictors of lower survival rate after re-OLT: recipient age [8–10], Model for End-Stage Liver Disease (MELD) score [8, 11, 12], donor age [8, 9, 12], and HCV infection [7, 9, 13, 14].

The relationship between recipient age and worst outcome after re-OLT is probably linked to the higher rate of associated comorbidities; in fact, Ghabril et al. [8] reported an increment of 1.52 of the risk of death every 20 years of increments in recipient age ($P=0.029$). Furthermore, considering only HCV-positive candidates for re-OLT, the International Liver Transplantation Society Expert Panel established that recipient age >55 years was associated with a worse outcome after re-OLT [9].

MELD score reflected the severity of graft dysfunction; in this sense, the higher the MELD score at the time of re-OLT, the lower the graft and patient survival rates. In particular, some authors reported both lower patient and graft survival rates in the case of a MELD score higher than 25 [8, 11]; during the first postoperative month, 48 % of patients with MELD >25 lost the second graft, compared to 16 % in the case of MELD <25 ($P<0.005$) [11]. In a cohort of 466 adult re-OLT recipients, Hong et al. reported a MELD score higher than 27 as an independent predictor of lower graft survival (hazard ratio (HR) 1.3; $P=0.031$) [12].

Donor age over 40 years (and particularly over 60 years) was strongly associated with graft failure after OLT, since it could be considered as an indirect parameter of the graft quality. Feng et al. reported a relative risk of graft failure equal to 1.53 (95 % confidence interval (CI) 1.39–1.68, $P<0.0001$) in the case of donor age higher than 60 years [15]. On the contrary, by maintaining cold ischemia time at 8 h or less, long-term graft function was shown to be equivalent in donors over and below 50 years of age [16]. In the case of re-OLT, the published literature agrees that the older the donors, the higher the risk of failure. In particular, donor age over or equal to 60 years was associated with a greater risk of patient death (HR 2.18; 95 % CI 1.25–3.8; $P=0.006$) [8], while donor age >45 years has been reported as an independent predictor of lower graft survival (HR 1.4; $P=0.018$) [12]. In the case of re-OLT due to HCV recurrence, donor age higher than 40 has been associated with the worst outcomes [9].

HCV infection has been related to lower graft and patient survival after both primary OLT and re-OLT [9]. In a cohort of 97 patients, Roayaie et al. found that patients undergoing re-OLT for recurrent HCV had a significantly shorter survival time when compared with patients undergoing a second transplant for other chronic causes of allograft failure ($P=0.0026$) [7]. Moreover, the severity of HCV recurrence is related to patient survival after re-OLT [9, 13, 14]; in fact, the mean survival time after re-OLT performed within 12 months was 16 months, compared to

45 months if re-OLT was performed later than 12 months after the first transplant ($P<0.05$) [13]. However, thanks to the newest antiviral treatment recently established [17, 18], the transplant community hopes that this *scenario* will be improved in a few years, due to the decrease of both HCV-related graft failure and HCV-related re-OLT.

Given the inferior outcome of re-OLT, several authors have created a model to guide clinicians in patient and donor selection, in order to optimize outcomes for this high-risk procedure. In particular, by combining INR, bilirubin, and time interval between primary and re-OLT, Rosen et al. have developed a mathematical model to predict patient survival after re-OLT; according to the risk score, patients were assigned to low-, medium-, and high-risk groups ($P<0.0001$) [19]. Furthermore, more recently, Hong et al. have created an index to exclude retransplant candidates on the basis of recipient age, MELD score, prior OLT >1, need for mechanical ventilation, serum albumin, donor age, intraoperative requirement of packed red blood cell transfusions, and interval between previous and re-OLT. According to the calculated score, re-OLT patients can be divided into four predictive risk categories (PCI); while in PCI I 5-year graft survival was 65 %, in PIC IV, it was 20 % ($P<0.001$) [12].

14.1 Primary Non-function

Early graft dysfunction could have a major impact on the prognosis and clinical outcome after OLT, with a reported incidence up to 23 % after deceased-donor OLT, in the current literature [20].

PNF is defined as a severe form of reperfusion injury, resulting in irreversible graft failure, without detectable technical or immunological problems [20–22]. It is still the most common reason for early re-OLT, with a reported incidence of 2–7 % in the recent literature [4, 20, 22]. PNF is manifested by hepatic cytolysis and rapidly rising transaminases, absence of bile production, severe liver-related coagulation deficit, hypoglycemia, high lactate levels, and hepatic hemodynamic instability. Early re-OLT is the only therapy for PNF.

The actual causes of PNF are still largely unknown, although some authors have demonstrated that disturbed microcirculation in the liver seems to play a key role in the development of PNF [23, 24]. There are several risk factors associated with PNF, such as prolonged ischemia time [4, 25], length of stay of the donor in the intensive care unit [4, 26], uncorrected donor hypernatremia [26, 27], increased donor age [4, 26, 28], and graft steatosis [4, 29]. Retransplanted patients had a much higher risk for PNF than those receiving primary OLT [4, 30]. These data suggest that PNF is caused not only by donor factors but also by recipient factors.

Five-year patient survival after re-OLT for PNF was comparable to that after re-OLT due to other causes (60 % versus 51 %; $P=0.635$) [4]. On the other hand, when PNF occurred in retransplant patients, their survival was very poor. In view of organ shortage, the wisdom of transplanting another graft after a retransplant for PNF should be carefully considered.

14.2 Vascular Complications

Hepatic artery thrombosis (HAT) is the most serious technical complication after OLT, occurring in approximately 2–9 % of cases [31–33] and frequently leading to patient death or re-OLT. Predisposing factors to HAT in whole OLT are technical aspects [31, 32], previous transarterial chemoembolization treatments [34], previous transplants [35], diabetes [36], cytomegalovirus infection [35], prolonged ischemia time [35], ABO incompatibility [37], acute rejection [37], Roux-en-Y biliary reconstruction [35], and transfusions [35]. The role of advanced donor age is controversial, with some studies showing no differences between younger and older donors and others reporting a higher prevalence of HAT with elderly donors; a large study within the United Network for Organ Sharing Registry reported a 61 % increased risk of HAT-related graft loss (relative risk = 1.61; $P<0.001$) with donors older than 70 years [38].

HAT occurs most commonly in the first 10 days after OLT, but it can present even many years later. The generally accepted definition of early HAT (eHAT) is thrombosis occurring within 1 month after OLT [39]; eHAT is often silent in the first phase and is frequently identified during a routine Doppler ultrasound examination. It should be suspected if there is a fever spike or transaminases alteration; if eHAT is unrecognized, it often leads to necrosis of the graft (Fig. 14.1) or serious complications secondary to the biliary tree necrosis.

On the other hand, late HAT, occurring more than 1 month after OLT, is a less common event and it may have a different evolution and outcome. This discrepancy in outcome between early and late HAT can be explained by the presence of arterial collaterals. After OLT, these collaterals (mainly derived from the phrenic arteries) are initially absent, but have been demonstrated angiographically as early as 2 weeks after OLT [40] (Fig. 14.2). Collaterals probably prevent biliary ischemic lesions in the case of late HAT [39, 40].

Factors reported to reduce the incidence of eHAT include the use of microvascular surgical techniques, the use of Doppler ultrasound (DUS) immediately after

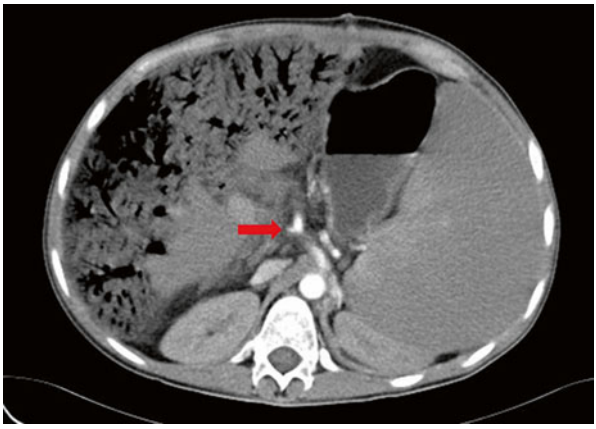

Fig. 14.1 Early postoperative hepatic artery thrombosis, which determined massive hepatic necrosis. The patient died awaiting re-OLT (*red arrow*: hepatic artery thrombosis)

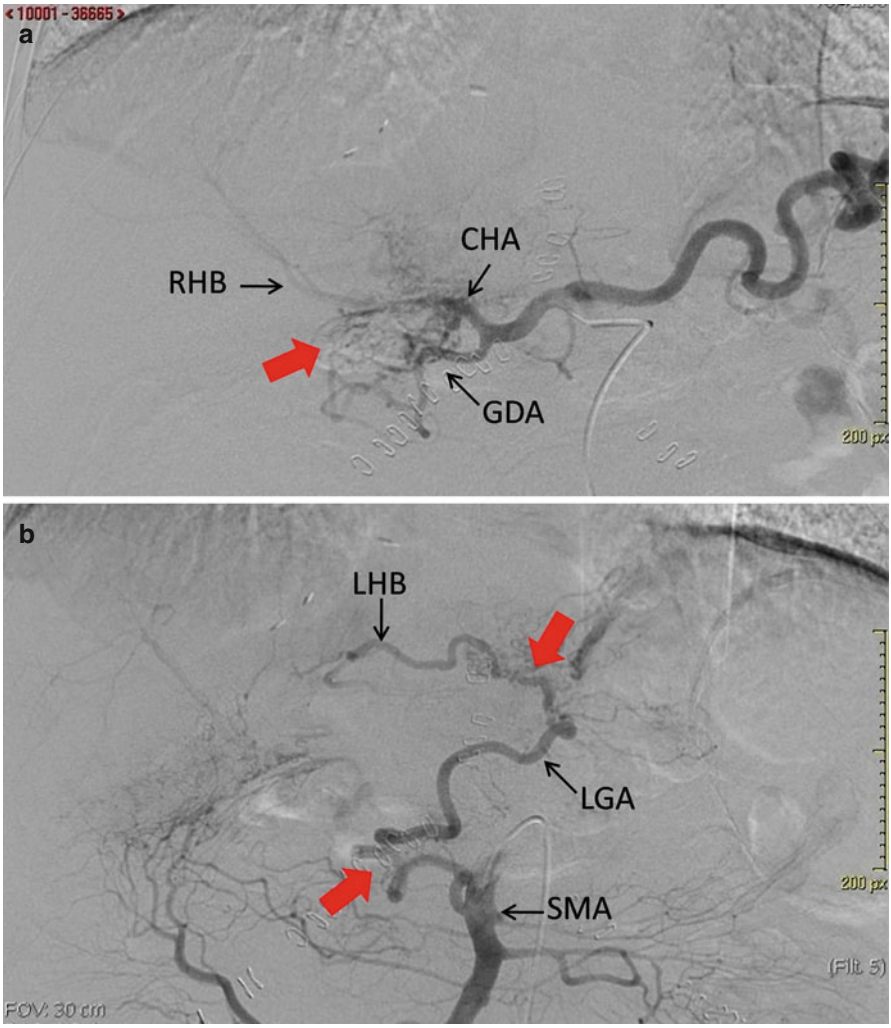

Fig. 14.2 Asymptomatic late hepatic artery thrombosis.(**a**) Selective angiography of the celiac trunk demonstrated common hepatic artery (*CHA*) thrombosis, with collateral arteries (*red arrow*) starting from the gastroduodenal artery (*GDA*), which revascularize the right hepatic branch (RHB). (**b**) Selective angiography of the superior mesenteric artery (*SMA*) demonstrated revascularization of the left gastric artery (*LGA*) and left hepatic branch (*LHB*) by collateral arteries (*red arrows*) starting from the SMA

surgery and daily scans for the first week, a low hematocrit, and the use of antiplatelet prophylaxis [31, 41]. The usual pattern of screening performed in our center is via routine DUS during the first postoperative week, while in cases of a suspicion of eHAT, a computed tomography angiography should be performed.

Various therapeutic options for managing HAT, including surgical revascularization [31, 32, 42, 43], portal vein arterialization [44], and endovascular treatments

[45], are available, but re-OLT is still the treatment of choice for HAT [39]; in fact, alternative procedures (both radiological and surgical) to re-OLT can be complicated by the occurrence of biliary complications, among which biliary cast syndrome (BCS) is the most fearful. BCS, first described in 1975, is defined as the presence of a hardened, dark material within the biliary ductal system that takes the physical shape of the bile ducts [46] and is clinically characterized by fever, jaundice, and cholestatic liver enzyme elevation. Although endoscopic/interventional radiology techniques are successful and safe in the removal of biliary casts [47], BCS can ultimately cause substantial injury to the liver, with some transplant recipients requiring re-OLT (Fig. 14.3).

The 1-year patient and graft survival rates after re-OLT for eHAT are 20–60 % [38, 45, 48] and 50 %, respectively [49]. Asymptomatic eHAT detected by DUS and treated with early revascularization shows promising results [31, 32, 41–44]. It is, however, important to detect eHAT while the patient is still asymptomatic, because graft survival after revascularization is much better in this group compared to symptomatic patients (81.8 % versus 40 %, respectively) [50].

Portal vein thrombosis (PVT) is a rare but severe complication that typically occurs early after OLT and is often related to abnormal venous reconstruction during surgery in patients with preexisting PVT [51] or to the presence of spontaneous/surgical portosystemic shunts determining graft hypoperfusion [52]; its incidence ranges from 2.1 to 13 % [51–54]. When PVT occurs soon after OLT, urgent surgical management may be necessary for PV thrombectomy or the placement of interposition grafts because allograft survival and potentially patient survival may be negatively affected without restoration of PV flow. Other possible approaches to PVT are percutaneous thrombolysis, angioplasty, and stent placement. Re-OLT is rarely

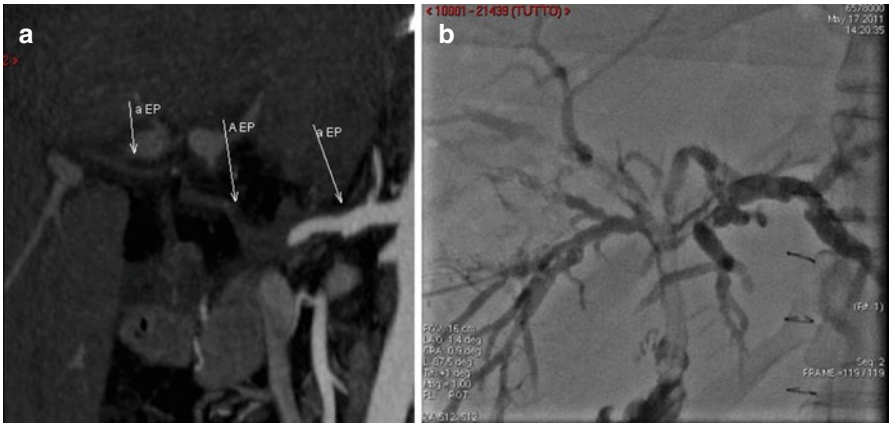

Fig. 14.3 (**a**) Early postoperative hepatic artery thrombosis, treated with surgical revascularization. (**b**) The patient developed biliary cast syndrome (note the multiple stenosis and filling defect of the biliary tree at cholangiography) that later required re-OLT (*white arrows*: hepatic artery course, prior to revascularization)

needed, especially in split-liver grafts/pediatric recipients experiencing early PVT, for the development of allograft failure [55].

Hepatic vein outflow obstruction after OLT is uncommon and occurs in less than 2 % of cases, but it is life-threatening if left untreated [56, 57]. The most common causes of hepatic vein thrombosis are anastomotic complications following OLT (30 %) [55]; although the majority of cases are managed conservatively with balloon angioplasty or transjugular intrahepatic portosystemic shunt placement, approximately 30 % of patients require re-OLT due to liver insufficiency [56].

14.3 Rejection

Nowadays, graft loss due to acute cellular rejection of the liver is an extremely rare condition, thanks to more effective immunosuppressive agents.

On the contrary, antibody-mediated rejection (AMR) has emerged as the cause of three types of rejection: (1) hyperacute rejection, (2) acute rejection, and (3) chronic rejection.

The hyperacute and acute forms of AMR are defined as acute rejection with graft dysfunction, histological evidence of acute tissue injury, and C4d deposition, in the presence of human leukocyte antigen donor-specific antibodies (DSA) [58]. The lack of interest in AMR in OLT is likely due to the fact that it is uncommon in liver recipients; however, in the last decade, a few cases of acute AMR after OLT have been reported [59]. O'Leary et al. have recently demonstrated that 5.8 % of previously unexplained early liver allograft loss was linked to AMR [60]; subsequently, the dosage of DSA is mandatory every time an unexplained graft dysfunction is present, in order to identify AMR early and promptly start the appropriate treatment, to avoid graft loss and the need for re-OLT [59–61].

Chronic rejection is the most common cause of late re-OLT [12, 19]. Thanks to advances in immunosuppressive therapy and to more sensitive means of detecting and diagnosing rejection, chronic rejection has considerably decreased in recent years as an indication for re-OLT, from 36 % at the end of the twentieth century to 9 % during the last few years [62].

14.4 Recurrence of Liver Disease

Hepatitis C virus recurrence accounts for 20–32 % of the cases of re-OLT, according to the most recent literature [7, 12–14, 62]. The indication for re-OLT for recurrent HCV-related allograft cirrhosis is still questionable, especially for the lower survival rate of these patients after re-OLT [7–9, 13].

However, the most recent literature agrees with the consideration that the timing of re-OLT performed for HCV recurrence is crucial to improve the outcome [13, 62, 63]. In particular, Marti et al. evaluated 108 patients who underwent nonurgent re-OLT adopting the Rosen score [19]. Only HCV-infected patients who developed cirrhosis at least 3 years after primary OLT underwent re-OLT. Applying these

selection criteria, the authors did not find significant differences in survival after re-OLT at 1, 5, and 10 years between patients with hepatitis C recurrence (70 %, 57 %, and 57 %, respectively) and all other causes (72 %, 50 %, and 45 %, respectively) [62]. Moreover, McCashland et al., applying the Rosen score, reported 1- and 3- year survival rates after re-OLT of 69 and 49 % for HCV-infected patients and 73 and 55 % for non-HCV-infected individuals, respectively [63].

OLT is a well-accepted treatment modality for autoimmune liver disease. Recurrence of primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and autoimmune hepatitis (AIH) after OLT has been widely described. While the impact of PBC recurrent disease on long-term survival after OLT is modest, with a re-OLT rate of 0.6–2 % [64, 65], PSC recurrence is very common, especially in the juvenile autoimmune form of sclerosing cholangitis (particularly if they have concurrent IBD), and it is associated with seriously compromised graft survival; in the case of PSC recurrence, a re-OLT rate of 5.4 % has been reported [66]. The AIH recurrence rate ranges from 12 to 46 % of cases [67]. Most patients with recurrent AIH respond to the reintroduction (or to an increase in dose) of corticosteroids and azathioprine, and re-OLT is a very rare event.

In conclusion, re-OLT is a high-risk procedure due to several early and late causes, weighted by an elevated rate of postoperative complications and a lower survival rate. In a context of organ shortage, it is mandatory to carefully select the patients who will benefit more from re-OLT, in order to avoid futile matches and graft loss.

References

1. Rana A, Petrowsky H, Kaplan B, Jie T, Porubsky M, Habib S, Rilo H, Gruessner AC, Gruessner RW. Early liver retransplantation in adults. Transpl Int. 2014;27:141–51.
2. Magee JC, Barr ML, Basadonna GP, Johnson MR, Mahadevan S, McBride MA, Schaubel DE, Leichtman AB. Repeat organ transplantation in the United States, 1996–2005. Am J Transplant. 2007;7:1424–33.
3. Busuttil RW, Farmer DG, Yersiz H, Hiatt JR, McDiarmid SV, Goldstein LI, Saab S, Han S, Durazo F, Weaver M, Cao C, Chen T, Lipshutz GS, Holt C, Gordon S, Gornbein J, Amersi F, Ghobrial RM. Analysis of long-term outcomes of 3200 liver transplantations over two decades: a single-center experience. Ann Surg. 2005;241:905–16.
4. Uemura T, Randall HB, Sanchez EQ, Ikegami T, Narasimhan G, McKenna GJ, Chinnakotla S, Levy MF, Goldstein RM, Klintmalm GB. Liver retransplantation for primary nonfunction: analysis of a 20-year single-center experience. Liver Transpl. 2007;13:227–33.
5. Azoulay D, Linhares MM, Huguet E, Delvart V, Castaing D, Adam R, Ichai P, Saliba F, Lemoine A, Samuel D, Bismuth H. Decision for retransplantation of the liver: an experience- and cost-based analysis. Ann Surg. 2002;236:713–21.
6. Doyle HR, Morelli F, McMichael J, Doria C, Aldrighetti L, Starzl TE, Marino IR. Hepatic retransplantation – an analysis of risk factors associated with outcome. Transplantation. 1996;61:1499–505.
7. Roayaie S, Schiano TD, Thung SN, Emre SH, Fishbein TM, Miller CM, Schwartz ME. Results of retransplantation for recurrent hepatitis C. Hepatology. 2003;38:1428–36.
8. Ghabril M, Dickson R, Wiesner R. Improving outcomes of liver retransplantation: an analysis of trends and the impact of hepatitis C infection. Am J Transplant. 2008;8:404–11.
9. Wiesner RH, Sorrell M, Villamil F. Report of the first International Liver Transplantation Society expert panel consensus conference on liver transplantation and hepatitis C. Liver Transpl. 2003;9:S1–9.

10. Rosen HR, Madden JP, Martin P. A model to predict survival following liver retransplantation. Hepatology. 1999;29:365–70.
11. Ravaioli M, Grazi GL, Ercolani G, Cescon M, Varotti G, Del Gaudio M, Vetrone G, Lauro A, Ballardini G, Pinna AD. Efficacy of MELD score in predicting survival after liver retransplantation. Transplant Proc. 2004;36:2748–9.
12. Hong JC, Kaldas FM, Kositamongkol P, Petrowsky H, Farmer DG, Markovic D, Hiatt JR, Busuttil RW. Predictive index for long-term survival after retransplantation of the liver in adult recipients: analysis of a 26-year experience in a single center. Ann Surg. 2011;254:444–8.
13. Ercolani G, Grazi GL, Ravaioli M, Del Gaudio M, Cescon M, Varotti G, Ramacciato G, Vetrone G, Zanello M, Pinna AD. Histological recurrent hepatitis C after liver transplantation: outcome and role of retransplantation. Liver Transpl. 2006;12:1104–11.
14. Martí J, De la Serna S, Crespo G, Forns X, Ferrer J, Fondevila C, Navasa M, Fuster J, García-Valdecasas JC. Graft and viral outcomes in retransplantation for hepatitis C virus recurrence and HCV primary liver transplantation: a case-control study. Clin Transplant. 2014;28:821–8.
15. Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, Greenstein SM, Merion RM. Characteristics associated with liver graft failure: the concept of a donor risk index. Am J Transplant. 2006;6:783–90.
16. Busuttil RW, Tanaka K. The utility of marginal donors in liver transplantation. Liver Transpl. 2003;9:651–63.
17. Belousova V, Abd-Rabou AA, Mousa SA. Recent advances and future directions in the management of hepatitis C infections. Pharmacol Ther. 2014;145:92–102.
18. Feeney ER, Chung RT. Antiviral treatment of hepatitis C. BMJ. 2014;348:g3308.
19. Rosen HR, Prieto M, Casanovas-Taltavull T, Cuervas-Mons V, Guckelberger O, Muiesan P, Strong RW, Bechstein WO, O'grady J, Zaman A, Chan B, Berenguer J, Williams R, Heaton N, Neuhaus P. Validation and refinement of survival models for liver retransplantation. Hepatology. 2003;38:460–9.
20. Chen XB, Xu MQ. Primary graft dysfunction after liver transplantation. Hepatobiliary Pancreat Dis Int. 2014;13:125–37.
21. Ploeg RJ, D'Alessandro AM, Knechtle SJ, Stegall MD, Pirsch JD, Hoffmann RM, Sasaki T, Sollinger HW, Belzer FO, Kalayoglu M. Risk factors for primary dysfunction after liver transplantation—a multivariate analysis. Transplantation. 1993;55:807–13.
22. Burton Jr JR, Rosen HR. Diagnosis and management of allograft failure. Clin Liver Dis. 2006;10:407–35.
23. Selzner M, Rudiger HA, Sindram D, Madden J, Clavien PA. Mechanisms of ischemic injury are different in the steatotic and normal rat liver. Hepatology. 2000;32:1280–8.
24. Sun CK, Zhang XY, Zimmermann A, Davis G, Wheatley AM. Effect of ischemia-reperfusion injury on the microcirculation of the steatotic liver of the Zucker rat. Transplantation. 2001;72:1625–31.
25. Strasberg SM, Howard TK, Molmenti EP, Hertl M. Selecting the donor liver: risk factors for poor function after orthotopic liver transplantation. Hepatology. 1994;20:829–38.
26. Fernández-Merino FJ, Nuño-Garza J, López-Hervás P, López-Buenadicha A, Moreno-Caparrós A, Quijano-Collazo Y, Sanjuanbenito A, Vicente-López E. Impact of donor, recipient, and graft features on the development of primary dysfunction in liver transplants. Transplant Proc. 2003;35:1793–4.
27. Totsuka E, Dodson F, Urakami A, Moras N, Ishii T, Lee MC, Gutierrez J, Gerardo M, Molmenti E, Fung JJ. Influence of high donor serum sodium levels on early postoperative graft function in human liver transplantation: effect of correction of donor hypernatremia. Liver Transplant Surg. 1999;5:421–8.
28. Detre KM, Lombardero M, Belle S, Beringer K, Breen T, Daily OP, Ascher NL. Influence of donor age on graft survival after liver transplantation—United Network for Organ Sharing Registry. Liver Transplant Surg. 1995;1:311–9.
29. Frongillo F, Avolio AW, Nure E, Mulè A, Pepe G, Magalini SC, Agnes S. Quantification of degree of steatosis in extended criteria donor grafts with standardized histologic techniques: implications for graft survival. Transplant Proc. 2009;41:1268–72.

30. Yoo HY, Maheshwari A, Thuluvath PJ. Retransplantation of liver: primary graft nonfunction and hepatitis C virus are associated with worse outcome. Liver Transpl. 2003;9:897–904.
31. Mourad MM, Liossis C, Gunson BK, Mergental H, Isaac J, Muiesan P, Mirza DF, Perera MT, Bramhall SR. Etiology and management of hepatic artery thrombosis after adult liver transplantation. Liver Transpl. 2014;20:713–23.
32. Del Gaudio M, Grazi GL, Ercolani G, Ravaioli M, Varotti G, Cescon M, Vetrone G, Ramacciato G, Pinna AD. Outcome of hepatic artery reconstruction in liver transplantation with an iliac arterial interposition graft. Clin Transplant. 2005;19:399–405.
33. Cescon M, Zanello M, Grazi GL, Cucchetti A, Ravaioli M, Ercolani G, Del Gaudio M, Lauro A, Morelli MC, Pinna AD. Impact of very advanced donor age on hepatic artery thrombosis after liver transplantation. Transplantation. 2011;92:439–45.
34. Panaro F, Ramos J, Gallix B, Mercier G, Herrero A, Niampa H, Pageaux GP, Navarro F. Hepatic artery complications following liver transplantation. Does preoperative chemoembolization impact the postoperative course? Clin Transplant. 2014;28:598–605.
35. Silva MA, Jambulingam PS, Gunson BK, Mayer D, Buckels JA, Mirza DF, Bramhall SR. Hepatic artery thrombosis following orthotopic liver transplantation: a 10-year experience form a single centre in the United Kingdom. Liver Transpl. 2006;12:146.
36. Moon JI, Barbeito R, Faradji RN, Gaynor JJ, Tzakis AG. Negative impact of new-onset diabetes mellitus on patient and graft survival after liver transplantation: long-term follow up. Transplantation. 2006;82:1625–8.
37. Toso C, Al-Qahtani M, Alsaif FA, Bigam DL, Meeberg GA, James Shapiro AM, Bain VG, Kneteman NM. AB0-incompatible liver transplantation for critically ill adult patients. Transpl Int. 2007;20:675–81.
38. Stewart ZA, Locke JE, Segev DL, Dagher NN, Singer AL, Montgomery RA, Cameron AM. Increased risk of graft loss from hepatic artery thrombosis after liver transplantation with older donors. Liver Transpl. 2009;15:1688–95.
39. Bekker J, Ploem S, de Jong KP. Early hepatic artery thrombosis after liver transplantation: a systematic review of the incidence, outcome and risk factors. Am J Transplant. 2009; 9:746–57.
40. Wozney P, Zajko AB, Bron KM, Point S, Starzl TE. Vascular complications after liver transplantation: a 5-year experience. AJR Am J Roentgenol. 1986;147:657–63.
41. Vivarelli M, La Barba G, Cucchetti A, Lauro A, Del Gaudio M, Ravaioli M, Grazi GL, Pinna AD. Can antiplatelet prophylaxis reduce the incidence of hepatic artery thrombosis after liver transplantation? Liver Transpl. 2007;13:651–4.
42. Langnas AN, Marujo W, Stratta RJ, Wood RP, Li SJ, Shaw BW. Hepatic allograft rescue following arterial thrombosis. Role of urgent revascularization. Transplantation. 1991;51:86–90.
43. Pinna AD, Smith CV, Furukawa H, Starzl TE, Fung JJ. Urgent revascularization of liver allografts after early hepatic artery thrombosis. Transplantation. 1996;62:1584–7.
44. Bhangui P, Salloum C, Lim C, Andreani P, Ariche A, Adam R, Castaing D, Kerba T, Azoulay D. Portal vein arterialization: a salvage procedure for a totally de-arterialized liver. The Paul Brousse Hospital experience. HPB (Oxford). 2014;16:723–38.
45. Singhal A, Stokes K, Sebastian A, Wright HI, Kohli V. Endovascular treatment of hepatic artery thrombosis following liver transplantation. Transpl Int. 2010;23:245–56.
46. Waldram R, Williams R, Calne RY. Bile composition and bile cast formation after transplantation of the liver in man. Transplantation. 1975;19:382–97.
47. Srinivasaiah N, Reddy MS, Balupuri S, Talbot D, Jaques B, Manas D. Biliary cast syndrome: literature review and a single centre experience in liver transplant recipients. Hepatobiliary Pancreat Dis Int. 2008;7:300–3.
48. Ghobrial RM, Farmer DG, Baquerizo A, Colquhoun S, Rosen HR, Yersiz H, Markmann JF, Drazan KE, Holt C, Imagawa D, Goldstein LI, Martin P, Busuttil RW. Orthotopic liver transplantation for hepatitis C: outcome, effect of immunosuppression, and causes of retransplantation during an 8-year single center experience. Ann Surg. 1999;229:824–31.
49. Washburn WK, Bradley J, Cosimi AB, Freeman RB, Hull D, Jenkins RL, Lewis WD, Lorber MI, Schweizer RT, Vacanti JP, Rohrer RJ. A regional experience with emergency liver transplantation. Transplantation. 1996;61:235–9.

50. Uzochukwu LN, Bluth EI, Smetherman DH, et al. Early postoperative hepatic sonography as a predictor of vascular and biliary complications in adult orthotopic liver transplant patients. AJR Am J Roentgenol. 2005;185:1558–70.
51. Uzochukwu LN, Bluth EI, Smetherman DH, Troxclair LA, Loss Jr GE, Cohen A, Eason JD. Selective revascularization of hepatic artery thromboses after liver transplantation improves patient and graft survival. Transplantation. 1997;64:1295–9.
52. Castillo-Suescun F, Oniscu GC, Hidalgo E. Hemodynamic consequences of spontaneous splenorenal shunts in deceased donor liver transplantation. Liver Transpl. 2011;17:891–5.
53. Lodhia N, Salem R, Levitsky J. Transjugular intrahepatic portosystemic shunt with thrombectomy for the treatment of portal vein thrombosis after liver transplantation. Dig Dis Sci. 2010;55:529–34.
54. Woo DH, Laberge JM, Gordon RL, Wilson MW, Kerlan Jr RK. Management of portal venous complications after liver transplantation. Tech Vasc Interv Radiol. 2007;10:233–9.
55. Jensen MK, Campbell KM, Alonso MH, Nathan JD, Ryckman FC, Tiao GM. Management and long-term consequences of portal vein thrombosis after liver transplantation in children. Liver Transpl. 2013;190:315–21.
56. Settmacher U, N€ussler NC, Glanemann M, Haase R, Heise M, Bechstein WO, Neuhaus P. Venous complications after orthotopic liver transplantation. Clin Transplant. 2000;14: 235–41.
57. Senzolo M, Patch D, Cholongitas E, Triantos C, Marelli L, Stigliano R, Dhillon A, Burroughs A. Severe venoocclusive disease after liver transplantation treated with transjugular intrahepatic portosystemic shunt. Transplantation. 2006;82:132–5.
58. Takemoto SK, Zeevi A, Feng S, Colvin RB, Jordan S, Kobashigawa J, Kupiec-Weglinski J, Matas A, Montgomery RA, Nickerson P, Platt JL, Rabb H, Thistlethwaite R, Tyan D, Delmonico FL. National conference to assess antibody-mediated rejection in solid organ transplantation. Am J Transplant. 2004;4:1033–41.
59. Paterno F, Shiller M, Tillery G, O'Leary JG, Susskind B, Trotter J, Klintmalm GB. Bortezomib for acute antibody-mediated rejection in liver transplantation. Am J Transplant. 2012;12:2526–31.
60. O'Leary JG, Kaneku H, Demetris AJ, Marr JD, Shiller SM, Susskind BM, Tillery GW, Terasaki PI, Klintmalm GB. Antibody-mediated rejection as a contributor to previously unexplained early liver allograft loss. Liver Transpl. 2014;20:218–27.
61. Schadde E, d'Alessandro AM, Musat AI, Torrealba JR, Knechtle SJ. Donor-specific HLA-antibody-mediated humoral rejection in a liver transplant recipient fully reversed with plasmapheresis and immunoglobulin. Clin Transpl. 2006:479–82.
62. Martí J, Charco R, Ferrer J, Calatayud D, Rimola A, Navasa M, Fondevila C, Fuster J, García-Valdecasas JC. Optimization of liver grafts in liver retransplantation: a European single-center experience. Surgery. 2008;144:762–9.
63. McCashland T, Watt K, Lyden E, Adams L, Charlton M, Smith AD, McGuire BM, Biggins SW, Neff G, Burton Jr JR, Vargas H, Donovan J, Trotter J, Faust T. Retransplantation for hepatitis C: results of a U.S. multicenter retransplant study. Liver Transpl. 2007;13:1246–53.
64. Jacob DA, Neumann UP, Bahra M, Langrehr JM, Neuhaus P. Liver transplantation for primary biliary cirrhosis: influence of primary immunosuppression on survival. Transplant Proc. 2005;37:1691–2.
65. Jacob DA, Neumann UP, Bahra M, Klupp J, Puhl G, Neuhaus R, Langrehr JM. Long-term follow-up after recurrence of primary biliary cirrhosis after liver transplantation in 100 patients. Clin Transplant. 2006;20:211–20.
66. Campsen J, Zimmerman MA, Trotter JF, Wachs M, Bak T, Steinberg T, Kam I. Clinically recurrent primary sclerosing cholangitis following liver transplantation: a time course. Liver Transpl. 2008;14:181–5.
67. Liberal R, Zen Y, Mieli-Vergani G, Vergani D. Liver transplantation and autoimmune liver diseases. Liver Transpl. 2013;19:1065–77.

Part III

Renal Transplantation

Indications and Timing

15

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Defining the clinical and metabolic *indications* and *timing* for transplant are key issues in all solid organ transplantations. In the case of kidney, the characteristics of both the organ and nephropathic patients make both the indications for *transplant* and its timing clearer and easier to establish than in other solid organs.

The *indication* for kidney transplant is chronic renal failure quantified on the basis of the residual glomerular filtration rate (GFR) reached by patients when treatment, if administered, has proved ineffective (Fig. 15.1) and changes to the renal parenchyma are definitive and irreversible. Given the multiple concomitant diseases present in these patients, due in part to their uremia and in part to dialysis, they require an in-depth analysis not only of the indications for transplant but also the contraindications, assessing the type and extent of the comorbidities affecting multiple organ systems.

To determine the *timing*, i.e., when to proceed to transplantation, a distinction must be made between theory and practice. In theory, transplant should be entertained when residual kidney function is around 10–15 %, irrespective of the start of regular dialysis treatment. However, this "early" optimal timing is only feasible if a living donor is available. In practice, almost all patients undergo kidney transplant when they have reached the terminal stage of uremia, the start of regular dialysis treatment (RDT), and placement on the renal transplant waiting list. The length of time spent on the waiting list will depend on organ availability and the number of patients awaiting transplantation.

In the United States, the number of people on the transplant waiting list has risen every year in the last decade, whereas the number of transplants has remained unchanged. During the same period, the average time on the waiting list before

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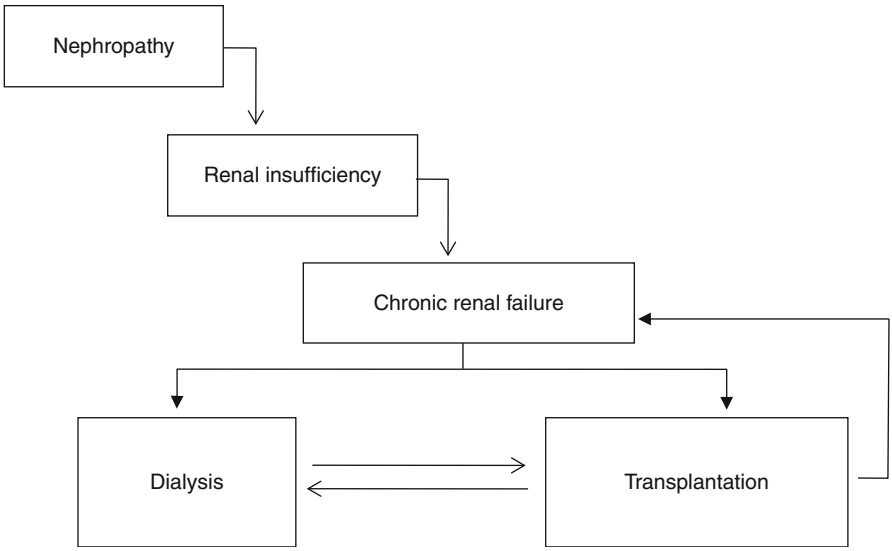

Fig. 15.1 Natural history of renal disease

transplantation rose to 2.7–4.2 years [1]. In Italy, the number of patients on the waiting list remained relatively stable in the same period (from 6,816 to 6,707) along with the number of transplants (from 1,487 to 1,501), with a high but stable average waiting time of 3.1 years [2].

The *indications* and *timing* for potential kidney transplant recipients include an assessment of transplantation *suitability*, any *contraindications*, and *monitoring* while on the waiting list. In addition to those related to surgery and immunology, many different aspects need to be addressed, not only those purely nephrological, but also those referring to other organs and systems.

From a *nephrological* standpoint, transplant candidates must have advanced chronic kidney disease (from stage 4) [3] or already be on dialysis treatment, as occurs in most cases. Tests should be carried out to identify the underlying kidney disease to determine any risks that may be particularly high in conditions like focal segmental glomerulosclerosis, uremic hemolytic syndrome, and primary oxalosis [4]. In addition, the type of dialysis treatment (hemodialysis or peritoneal dialysis) must be considered together with its depurative efficacy, paying special attention to the patient's nutritional status.

Age is an important parameter: recent decades have seen a marked increase in the number of elderly patients on the waiting list for transplantation. While patients aged over 65 years accounted for 36 % of those on the transplant waiting list in the United States in the 1980s, this percentage had risen to 48 % in 2009; 36 % of new patients with end-stage renal disease are currently aged over 70 years [5–7]. Age itself is not a contraindication to kidney transplant. Although elderly patients have a more than twofold risk of dying in the perioperative period [8] and a high risk of

cancer, cardiovascular events, and infections, they have a survival advantage of 61 % with respect to remaining on the transplant waiting list, with an increased life expectancy of around 4 years [9] compared with continued RDT.

Many *urological* indications must be addressed before transplantation. Any abnormalities or diseases can be treated before transplant, carefully weighing the risks and benefits in each individual case [10, 11].

In particular, the progressive contraction of diuresis common in many patients after years of dialysis may lead to reduced bladder capacity and hypertrophy of the detrusor muscle. Possible removal of the native kidneys must also be entertained especially in patients with polycystic disease (increased abdominal burden, hemorrhage, lithiasis, or infection) or infected lithiasis [11, 12].

In establishing the indications for kidney transplant, assessment of the *cardiovascular apparatus* is essential as it is the prime cause of death after transplantation in both the short and long term [5, 13]. In-depth history taking should be followed by tests including cardiac examination, basal ECG, and chest x-ray. An echocardiogram is also useful to determine left ventricular hypertrophy, dilatation, and valve disorders. The latest guidelines of the American College of Cardiology/American Heart Association [14] suggest using noninvasive stress tests in patients without active heart problems but with at least three of the following risk factors: age over 60 years, more than 1 year of dialysis, diabetes mellitus, previous *cardiovascular* disease, hypertension, dyslipidemia, and smoking. The European guidelines [11] recommend pharmacological stress testing by ultrasound scan or scintigraphy in patients with a positive or inconclusive stress test. Coronarography is indicated in patients presenting features of inducible ischemia.

Any signs or symptoms of *cerebrovascular* or *peripheral vascular disease* must also be evaluated. If stenosis of the large vessels is suspected, angiography may be indicated possibly followed by endoscopic treatment, especially in patients with clinical symptoms [15].

Uremic patients have a higher incidence of *cancer* than the general population [16, 17]. There is a general consensus on the need to investigate patients on entry onto the transplant waiting list, even though shared screening protocols are currently lacking. The latest European guidelines suggest patients undergo the same screening tests indicated for the general population, mainly to search for any renal tumors, especially in patients on dialysis for many years. Hepatocellular carcinoma should be ruled out in patients with HCV and HBV infection [11, 18]. The American guidelines emphasize the use of the PAP test and a gynecological examination at least every 3 years in women after the age of 20 years, an annual breast examination and mammogram after the age of 40 years, thyroid gland assessment, a search for fecal occult blood after the age of 50 years, and rectal exploration with PSA measurement in men over 50 years [12]. A *cancer* screening protocol was recently published in Italy for patients on the waiting list for kidney transplantation [16].

Patients with a *history of cancer* need to be assessed on a case-by-case basis for entry onto the transplant waiting list, with a multidisciplinary approach also involving the cancer specialist.

A series of indications and recommendations have been published on the length of the waiting period following diagnosis and treatment of cancer, designed to harmonize decision-making in different transplant centers [19].

Active *infection* may require eradication or prophylactic interventions before transplant or the inclusion of these patients in special transplantation programs.

The indications for kidney transplant also include serologic tests for HIV infection, hepatitis B and C, herpes simplex, HHV-8, varicella zoster, rubella, EBV, CMV, *Toxoplasma gondii*, and syphilis and the Mantoux test. If a second transplant is envisaged, the BK virus should also be investigated.

Currently, around 1 % of patients on dialysis in the United States present HIV *infection* [20]. This condition initially represented an absolute contraindication to transplant as these patients had a limited life expectancy and a high incidence of opportunistic infections. Nowadays, indications can be put in place for transplantation in patients compliant with specific treatment, a CD4+ cell count above 200/μL and a viral load undetectable for at least 3–6 months, with no opportunistic infection in the past 6 months and no signs of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis, or lymphomas. Posttransplant antiretroviral therapy must be defined in the light of its possible competitive effects with immunosuppressants [11, 21].

Patients with hepatitis B and C virus have a better survival rate with kidney transplant than dialysis. However, their postoperative course can be complicated by an increased incidence of HCV-related renal disease, new-onset diabetes mellitus, and shorter graft/patient survival rates. Patients with decompensated liver disease can be assessed for the combined liver-kidney transplant program [22, 23].

CMV and EBV serology are crucial for posttransplant decision-making. CMV infection is a risk factor for graft failure, *infection*, the onset of lymphoproliferative disease, cardiovascular events, diabetes mellitus, and acute graft rejection [24].

Patients positive for EBV are considered at high risk for the development of lymphoproliferative disease: the indications for transplant include a very cautious management of immunosuppressive therapy, with serological monitoring before transplant possibly including antiviral prophylaxis [12]. Vaccination is recommended before transplant in patients negative for herpes-varicella zoster virus [25] and in rubella-negative women of fertile age given the likelihood of future pregnancy [26].

The increase in the immigrant population has led to a resurgence of tuberculosis. The Mantoux test must be administered in all kidney transplant candidates together with chest x-ray. Prophylaxis is advisable in the case of latent tuberculosis while active forms of tuberculosis require appropriate specific treatment before any indication for kidney transplantation.

Many centers also undertake a dental assessment prior to transplant to treat any infection of the teeth or gums [12].

Diabetes mellitus is currently the most common cause of chronic kidney failure in the United States and increasingly one of the most common in Europe and Italy. Diabetic patients merit special attention in establishing an indication for kidney transplant due to the high incidence of associated *comorbidities*: cardiovascular and dysmetabolic abnormalities, risk of infection, neurological impairment, peripheral

vascular disease, etc. A combined kidney-pancreas transplant is the best option in insulin-dependent diabetes patients to normalize glucose metabolism [27, 28].

Obesity has now reached epidemic proportions in the developed countries and has not spared patients with chronic kidney disease. In 2011, 23 % of patients in the US kidney transplant waiting lists were obese. *Obesity* is correlated to longer surgery times and hospital stay, an increased recourse to intensive care, and a higher incidence of surgical wound-healing problems. An elevated body mass index is also correlated to delayed functional recovery of the transplanted organ with an increased risk of graft loss [29]. The international guidelines for kidney transplant indication in obese patients suggest diet and physical exercise programs [11, 12].

In relation to the *gastrointestinal* apparatus, the search for *intestinal* diverticular disease is particularly important given its frequency in patients on dialysis, especially those with hepatorenal polycystic disease [30]. Diverticulitis is the most common cause of posttransplant intestinal perforation (0.5–2 %), correlated with a very high mortality rate (17–43 %). Patients with a history of diverticulitis must be investigated endoscopically, bearing in mind gut resection in the case of extensive or symptomatic disease. Peptic ulcer used to be common (18–40 %), but the widespread use of proton pump inhibitors has drastically reduced its incidence. Nonetheless, *gastric* endoscopy with a search for *Helicobacter pylori* is advisable flanked by ultrasound gallbladder examination and possible assessment of ablation in patients with calculi due to the risk of posttransplant acute cholecystitis [12].

The *respiratory apparatus* should be screened for unchangeable risk factors with intervention on factors that can be rectified. Patients must be strongly encouraged to quit smoking as smokers have a 5.5 higher risk of developing lung complications than nonsmokers [12].

Among the indications for kidney transplant, *psychosocial* assessment should disclose any behavioral traits in the graft recipient likely to undermine the success of transplantation. The results of psychometric testing are most useful when combined with a clinical interview and other sources of patient information. Specific screening tools like the *psychological assessment* of candidates for transplantation (PACT) scale and the transplantation evaluation rating scale (TERS) may also prove useful [31]. Cognitive dysfunction does not in itself rule our eligibility for transplantation. If the candidate cannot provide his/her informed consent, a family support system should be sought to ensure compliance with drug management and the necessary posttransplant follow-up [12]. Patients with active alcohol or drug addiction must be referred to a detoxification program. If the course is successful, a period of abstinence of at least 6 months is required before reassessing the patient for transplant eligibility.

15.1 Monitoring Patients on the Transplant Waiting List

Once the *indications* for transplantation have been established and the patient carefully vetted, the wait for a potential donor begins. This is a dynamic rather than static process. Because of the length of time spent on the waiting list, patients have

to be monitored to disclose the onset of any clinical problems that could temporarily or definitively exclude them from transplantation. In the United States, around 30 % of patients are *excluded* from the waiting list at some point, at least temporarily [32]. The American guidelines recommend *monitoring* patients' health conditions at least every 2 years [12] while *high-risk patients* (diabetes, aged over 65 years, cardiovascular disease, etc.) must be reassessed more often. The frequency and type of diagnostic laboratory and instrumental tests needed to ascertain the persistence of transplant *indications* and to optimize the *timing* of transplantation are requested by transplant centers on the basis of experience and clinical practice as there is currently no general consensus in the literature.

References

1. Matas AJ, Smith JM, Skeans MA, Thompson B, Gustafson SK, Schnitzler MA, et al. OPTN/SRTR 2012 annual data report: kidney. Am J Transplant. 2014;14 Suppl 1:11–44.
2. Centro Nazionale Trapianti – Ministero della Salute: http://www.trapianti.salute.gov.it/cnt/cnt-Statistiche. Accessed 10 June 2014.
3. Danovitch GM. Handbook of kidney transplantation. 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2005.
4. Chadban SJ, Vacher-Coponat H. Recurrent disease in kidney transplantation. In: Floege J, Johnson RJ, Feehally J, editors. Comprehensive clinical nephrology. 4th ed. Philadelphia: Elsevier Saunders; 2010. p. 1211–21.
5. United States Renal Data System (USRDS): http://www.usrds.org/2013. Accessed 10 June 2014.
6. Knoll GA. Kidney transplantation in the older adult. Am J Kidney Dis. 2013;61(5):790–7.
7. Rao PS, Merion RM, Ashby VB, Port FK, Wolfe RA, Kayler LK. Renal transplantation in elderly patients older than 70 years of age: results from the Scientific Registry of Transplant Recipients. Transplantation. 2007;83(8):1069–74.
8. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation and recipients of a first cadaveric transplant. NEJM. 1999;341:1725–30.
9. Lenihan CR, Hurley MP, Tan JC. Comorbidities and kidney transplant evaluation in the elderly. Am J Nephrol. 2013;38(3):204–11.
10. Silva DM, Prudente AC, Mazzali M, Borges CF, D'Ancona C. Bladder function evaluation before renal transplantation in nonurologic disease: is it necessary? Urology. 2014;83(2):406–10.
11. European Renal Best Practice Transplantation Guideline Development Group. ERBP Guideline on the management and evaluation of the kidney donor and recipient. Nephrol Dial Transplant. 2013;28 Suppl 2:1–71.
12. Kasiske BL, Cangro CB, Hariharan S, Hricik DE, Kerman RH, Roth D, et al. American Society of Transplantation. The evaluation of renal transplantation candidates: clinical practice guidelines. Am J Transplant. 2001;1 Suppl 2:3–95.
13. Ojo AO. Cardiovascular complications after renal transplantation and their prevention. Transplantation. 2006;82(5):603–11.
14. Lentine KL, Costa SP, Weir ML, Robb JF, Fleischer LA, Kasiske BL, et al. Cardiac disease evaluation and management among kidney and liver transplantation candidate a scientific statement from the American Heart Association and the American College of Cardiology Foundation. Circulation. 2012;126:617–63.
15. Sung RS, Althoen M, Howell TA, Merion RM. Peripheral vascular occlusive disease in renal transplant recipients: risk factors and impact on kidney allograft survival. Transplantation. 2000;70(7):1049–54.

16. Mosconi G, Centofanti F, Capelli I, Ricci A, Persici E, Gandolfini I, et al. Incidence and prevalence of cancer in kidney transplantation waiting list patients: an Italian experience. Int J Artif Organs. 2013;36(5):335–40.
17. Piselli P, Serraino D, Segoloni GP, Sandrini S, Piredda GB, Scolari MP, et al. Risk of de novo cancers after transplantation: results from a cohort of 7217 kidney transplant recipients, Italy 1997–2009. Eur J Cancer. 2013;49(2):336–44.
18. European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56(4):908–43.
19. Campistol JM, Cuervas-Mons V, Manito N, Almenar L, Arias M, Casafont F, et al. New concepts and best practices for management of pre- and post-transplantation cancer. Transplant Rev. 2012;26(4):261–79.
20. Trullas JC, Cofan F, Tuset M, Ricart MJ, Brunet M, Cervera C, et al. Renal transplantation in HIV-infected patients: 2010 update. Kidney Int. 2011;79:825–43.
21. Campbell S, Pilmore H, Gracey D, Mulley W, Russell C, McTaggart S, et al. KHA-CARI guideline: recipient assessment for transplantation. Nephrology. 2013;18(6):455–62.
22. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. Kidney Int. 2008;109:S1–99.
23. Covic A, Abramowicz D, Bruchfeld A, Leroux-Roels G, Samuel D, van Biesen W, et al. Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) hepatitis C guidelines: a European Renal Best Practice (ERBP) position statement. Nephrol Dial Transplant. 2009;24(3):719–27.
24. Kotton CN, Kumar D, Caliendo AM, Asberg A, Chou S, Danziger-Isakov L, et al. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation. 2013;96(4):333–60.
25. Broyer M, Tete MJ, Guest G, Gagnadoux MF, Rouzioux C. Varicella and zoster in children after kidney transplantation: long-term results of vaccination. Pediatrics. 1997;99(1):35–9.
26. Kasiske BL, Zeier MG, Chapman JR, Craig JC, Ekberg H, Garvey CA, et al. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. Kidney Int. 2010;77(4):299–311.
27. Ponticelli C. Medical complication of kidney transplantation. Abingdon: Informa Healthcare; 2007.
28. Jiang AT, Rowe N, Sener A, Luke P, BHSc. Simultaneous pancreas-kidney transplantation: the role in the treatment of type 1 diabetes and end-stage renal disease. Can Urol Assoc J. 2014;8(3–4):135–8.
29. Lentine KL, Delos Santos R, Axelrod D, Schnitzler MA, Brennan DC, Tuttle-Newhall JE, et al. Obesity and kidney transplant candidates: how big is too big for transplantation? Am J Nephrol. 2012;36(6):575–86.
30. Pourfarziani V, Mousavi-Nayeeni SM, Ghaheri H, Assari S, Saadat SH, Panahi F, et al. The outcome of diverticulosis in kidney recipients with polycystic kidney disease. Transplant Proc. 2007;39(4):1054–6.
31. Jowsey SG, Taylor ML, Schneekloth TD, Clark MM. Psychosocial challenges in transplantation. J Psychiatr Pract. 2001;7(6):404–14.
32. Shafi S, Zimmerman B, Kail R. Temporary inactive status on renal transplant waiting list: causes, risk factors and outcomes. Transplant Proc. 2012;44:1236–40.

Renal Transplantation: Kidney Procurement from Cadaveric Donors

16

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In most cases, kidney retrieval is just part of a complex procedure such as multiorgan procurement where different surgical teams have to work together and collaborate to reach a common aim, which means getting the best result for as many potential recipients as possible. Each member of the retrieval team has to know the entire procedure in order to retrieve viable grafts, taking care of both anatomic aspects and preservation quality.

Multiorgan procurement is a well-codified surgical procedure with standardized phases, the basis of which was first described by Starzl in 1984 [1]. Communication and respect for colleagues and the donor are the key points for a good result.

Once thorough thoracic and abdominal exploration and exposure of the vascular pedicles of the grafts have been completed (see also Chap. 8), it is time for cross-clamping. The common iliac arteries should also be explored before cross-clamping to identify any additional renal vessels that may originate from there. The aorta is usually cannulated just above the iliac bifurcation and then clamped in the supraceliac position; cold perfusion is initiated in agreement with the cardiothoracic team. The inferior vena cava (IVC) or right atrium is transected for venous drainage to facilitate continuous high-flow perfusion. During the harvesting of the thoracic organs, the abdominal cavity is entirely chilled with slushed ice to associate the core cooling of the systemic perfusion with the topical action of the ice.

Removal of thoracic organs, liver, and pancreas generally precedes retrieval of the kidneys. It is very important to avoid rewarming of the kidneys during this time. Mobilization of the ascending and descending colon is advisable in order to allow a more direct exposure of the kidneys to ice. A complete exposure of the inferior vena

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cava to the origin of the left renal vein using a Kocher maneuver is indicated; this makes possible to visualize possible venous variations of the renal hilum and to perform a proper sectioning of the IVC a few millimeters above to the origin of the right renal vein in order to maintain enough tissue for elongation of a short right renal vein if needed.

Special care must also be taken during the sectioning of the aorta when the liver and pancreas are retrieved because this is probably the most likely time when a renal artery is accidentally detached from the aortic patch. Sectioning of the aorta, usually performed by the liver or pancreas team, should be done just below the origin of the superior mesenteric artery approaching the anterior wall of the aorta with an oblique angle so as to identify, and not injure, the renal arteries.

After the retrieval of the thoracic organs, liver, and pancreas, it is time for the kidney retrieval team to start. The small bowel is pulled into the upper abdomen packed in a large swab; the empty abdomen facilitates kidney retrieval.

Surgeons should be aware of the possible anatomical variations that they may face: frequent vascular variations (multiple vessels, retroaortic left renal vein, anomalous venous drainage), urologic variations (double renal pelvis, multiple ureters), or variable kidney position (pelvic kidney or absent kidney, horseshoe kidney). In most of the cases, these are not detected at the preoperative workup. A horseshoe kidney does not represent a contraindication for transplant in itself (it can be transplanted to a single recipient en bloc or into two patients after division of the renal isthmus), but it exposes the surgeon to a new technical challenge because of the complexity of the vascular anatomy [2]. The isthmus can be a fibrous band or may contain functional parenchyma; the multiple renal vessels often originate from iliac arteries and veins while the renal isthmus may have an independent blood supply.

Kidneys retrieval can be performed either individually, dividing the vascular pedicle in situ, or en bloc. En bloc kidney retrieval, which will be briefly described later, is more often used in pediatric donors especially when a dual kidney transplant with aortic and caval anastomosis is planned. Kidney harvesting starts with the bilateral identification of the ureter and its isolation together with the gonadal veins and the fat tissue between them. The ureter is transected proximally to the bladder and dissected along an avascular plane on the psoas muscle; it is of paramount importance to preserve the tissue surrounding the ureter and the triangle between the lower pole of the kidney and the ureter, minimizing the risk of devascularizing the ureter. The aorta and IVC are then transected inferiorly at the level of cannulation.

When explanted separately, the left renal vein is divided at the origin from the IVC; the right kidney is removed with all the remaining vena cava to preserve a conduit to extend the right renal vein if needed; the IVC is then mobilized toward the right kidney, taking care at the right renal artery which lies just behind it. Once the exposure of the aorta and the bilateral origins of the renal arteries has been completed, a midline incision is made on the anterior wall of the aorta. Inspection of the interior surface makes it possible to identify orifices of renal arteries (and also of any potential ones) and guides the longitudinal sectioning of the posterior wall; it is

important to maintain adequate aortic tissue around each vessel to allow Carrel patch fashioning.

Some surgeons prefer to also divide the IVC longitudinally in a symmetric way, advocating the same advantages as those described for aorta; others leave just a cuff of vena cava with left renal vein to ensure a comfortable anastomosis.

The vascular pedicles are now completely separated; dissection on the paravertebral plane, starting from the midline to the lateral profile of the kidney, guarantees avoiding injury of the vascular structures even in the case of multiple vessels. All the tissue situated posterior to the aorta is divided. The upper line of sectioning is made in the adrenal gland to preserve the polar arteries. The kidney is now detached from the retroperitoneum following the avascular plane of the Gerota fascia and then removed. It can easily be removed from the donor together with the pararenal fat, but it is highly advisable to incise the surrounding fat in order to permit a proper cooling of the kidney and a complete exploration of the parenchymal surface.

The shortage of available organs for transplant has led to the use of older donors with a consequent greater degree of atheroma. More caution and gentle surgery are recommended in this kind of donor. An atheromatous aorta can make the placement of the aortic cannula difficult and dangerous especially in the case of an aortic aneurysm. Direct mechanical trauma of the arterial wall and the high pressure of perfusion can cause the atheroma material to break and can lead to cholesterol embolization which may affect the future kidney function in the recipient [3, 4]. The quite frequent presence of atheromatous stenosis of the renal artery origin does not represent a contraindication for transplant in itself but requires careful cannulation during bench surgery to better flush the kidney and cool the graft, avoiding intimal damage. Avulsion injuries are also described due to intimal or adventitial tear in fragile and easily dissectible vessels.

Once it has been removed, the graft is then immediately placed in cold preservation solution for a preliminary bench check and additional perfusion. The same procedure is repeated for the contralateral kidney.

Arterial and venous grafts (usually iliac or carotid vessels) for reconstruction during liver, pancreas, or kidney transplant can now be retrieved. Small samples of spleen and mesenteric lymph nodes are often required for histocompatibility testing (crossmatch between donor lymphocytes and recipient serum). Tight and cosmetic closure of the abdomen and thorax is advisable as a matter of respect toward the donor's family.

Gerota fascia must be opened on the back table and the perirenal fat removed to carefully inspect the parenchyma and allow more efficient cooling. In older donors, especially if smokers or with a history of renal inflammation, the perirenal fat can sometimes be tightly adherent to the capsule; in that case, it is preferable to leave some portions of adherent fat (which could be carefully removed later by the transplant team) to avoid the risk of entering a subcapsular plane and determining further bleeding or parenchymal damage. Simple cysts are quite common; the presence of solid lesions or complex cysts suspected of being tumors, even if not detected at the preoperative ultrasound, must not be ignored; an immediate complete excision and pathological examination are mandatory. All the teams should be promptly informed

about the presence of potential cancer. Preliminary examination of the vascular anatomy avoiding excessive dissection into the hilum and a further ex situ flushing with cold solution directly in the renal artery are recommended until the output from the renal vein becomes clear.

A preimplantation biopsy is commonly performed by many centers especially for comparison with subsequent samples. This can be a needl biopsy or a punch or a wedge biopsy. The common aim is to take out a sample of cortex with a sufficient number of renal glomerulus, without going too deep into the medulla which is not useful for pathologic diagnosis and may determine severe bleeding or create arterial-venous fistulas or urinary fistulas. In the so-called marginal donors, the preimplantation kidney biopsy plays a central role in the process of valuation of the quality of the kidney. As described in more detail in Chap. 20, donor parameters are integrated with anatomo-pathological features in the process of evaluating the suitability of the graft to enlarge the pool of suitable kidneys and to optimize the use of kidneys from older donors as single or dual transplants. We suggest performing the kidney biopsy immediately after the exploration of the abdominal cavity during the heartbeating phase when the donor is hemodynamically stable instead of doing it after the kidney retrieval. Kidney biopsies can be sent to the pathologist together with samples of the liver and suspicious lesions that may be detected. The advantages obtained by earlier identification of the candidate for transplant (single or dual on the basis of pathological findings), the shortening of the cold ischemic time, and the economic saving compensate the minimal lengthening of the procedure caused by biopsying a not yet exposed kidney in a heartbeating donor with potential risk of bleeding.

Having completed the bench perfusion, the kidneys can then be preserved either in standard cold storage or in continuous machine perfusion and sent to the transplant unit. Continuous machine perfusion offers persistent and homogenous core cooling that mimics the physiological pulsate blood flow and seems to offer better results compared to static hypothermic preservation.

Because in most cases the retrieval surgeon and the transplant surgeon belong to different teams, it is good practice to produce a document reporting essential information regarding the donor, cross-clamping time, and the graft (kidney size, macroscopically detectable global quality of the kidney and of the degree of perfusion, vascular and ureteral anatomy in terms of numbers, caliber, length, presence/absence of patch and quality, injuries if present, type, and volume of the perfusion solution used).

En bloc removal of the kidneys is performed with the same accuracy as single kidney removal. Once the aorta and vena cava have been divided at a subceliac level cranially and just before the iliac bifurcation caudally, inferior to superior dissection is performed posterior to the aorta and vena cava. Ureters should be isolated before this stage. After their removal, separation of the kidneys is performed on the back table following the same criteria of leaving the vena cava with the right kidney and enough aortic patch for all renal arteries.

16.1 Bench Surgery

Bench surgery has two basic aims: to prepare the vessels for safe fashioning of the anastomosis and to ensure good hemostasis in order to avoid massive bleeding during the reperfusion of the graft. It is crucial to find the right depth at which to stop the dissection in the hilum: this is the result of a balance between obtaining a satisfactory length of the vessels to ensure a safe anastomosis and getting too deep into the hilum with the risk of causing damage that is difficult to repair.

The kidney, placed in a basin in the anatomical position, is kept cold by slushed ice which never comes in direct contact with the graft (Figs. 16.1 and 16.2).

The renal vein and the IVC are dissected free of the extra tissue, and gonadal, adrenal, and any other veins coming from extrarenal tissue are ligated and divided. A similar procedure is performed with the renal artery taking into account that even small branches coming from the main artery are likely to supply the kidney (it is very unusual to find branches which do not go to the parenchyma).

An accurate dissection between ligations is recommended not only to obtain good hemostasis once the clamps in the recipient have been released but also to close lymphatic vessels and to limit the incidence of lymphorrhagia and lymphocele posttransplant [5].

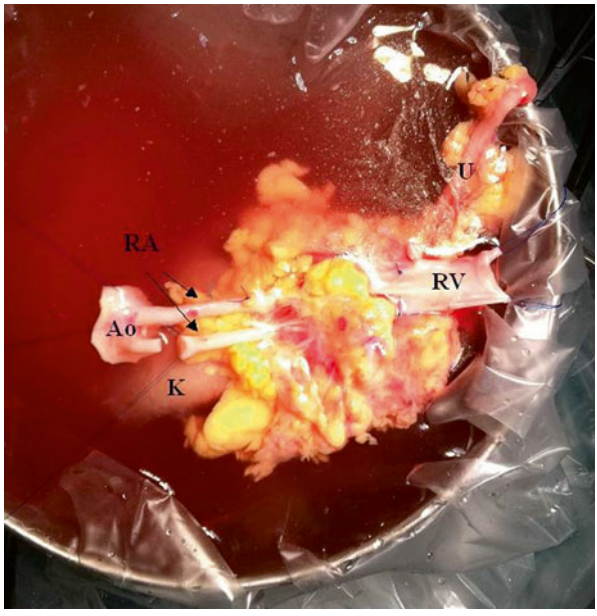

Fig. 16.1 *Right* kidney in the basin during bench surgery. One of the two renal arteries (*RA*) has been accidentally sectioned from its origin during the retrieval. *Ao* aorta, *RV* renal vein, *U* ureter, *K* renal parenchyma

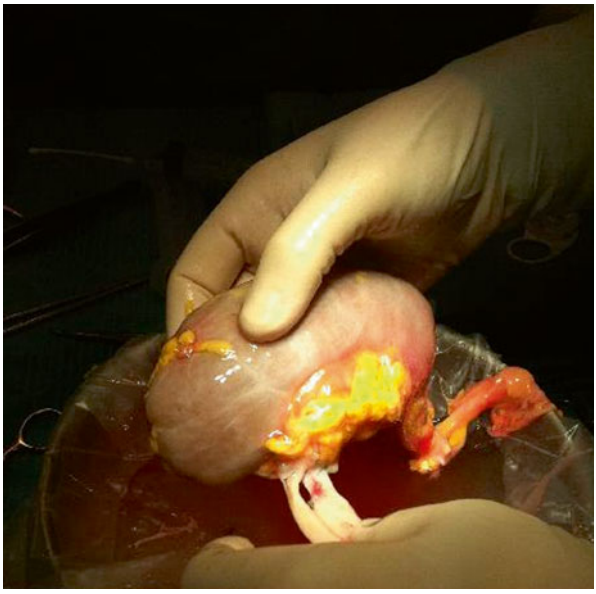

Fig. 16.2 The renal graft once the bench surgery has been completed. The renal artery and the vein have been dissected free of the extra tissue. The paraureteral fat has been preserved as well as the hilar fat

16.1.1 Kidney Preservation

Despite the significant increase in live donor kidney transplantation over the past 20 years, the number of patients awaiting transplant continues to rise [6]. In order to expand the pool of available donors, all the fields of science related to the process of donation/transplantation have been the subject of renewed interest in the last decade. Particular attention has recently been focused on the importance of preservation of grafts, especially of those obtained from marginal donors. Hypothermia allows the cellular metabolism to adapt itself to the anoxy condition (at 4 °C, the metabolism decreases by about 95 %); the drop in the energy consumption is also associated with the reduction of the activity of hydrolytic enzymes (proteases, phospholipases, nucleases) which limits structural cellular damage to the graft. Even if no firm recommendations establish the optimum method of renal preservation [7], some recent reports advocate certain advantages in terms of reduced incidence of delayed graft function and 1-year graft survival of machine perfusion when compared with static cold storage [8–11]. Even if the results of recent studies appear not quite homogenous, there appears to be enough benefit associated with pulsate preservation to justify its continued use in routine clinical practice. A perfusion machine, measuring parameters such as renal resistances, may also offer a prognostic value that, in the near future, together with pathologic and clinical features could become part of the evaluation of the graft and contribute to the allocation process. Further adequately powered randomized studies are required in both heartbeating and non-heartbeating donors, standard criteria donor, and expanded criteria donors using standardized perfusion fluid, in order to estimate the real advantage in specific and homogenous subgroups of donors.

The classic concept of hypothermia as the best method of organ and tissue preservation is now a subject of debate. After a large amount of experimental research, normothermic perfusion is now being implemented as a novel method of preservation that restores circulation and allows an organ to regain function prior to transplantation. Encouraging results come from earlier clinical experiences in grafts obtained from expanded criteria donor [12].

References

1. Starzl TE, Hakala TR, Shaw BW, et al. A flexible procedure for multiple cadaveric organ procurement. J Surg Gynecol Obstet. 1984;158(3):223–30.
2. Pontinen T, Khanmorandi K, Kumar, et al. A horseshoes kidneys: an underutilized resource in kidney transplant. Exp Clin Transplant. 2010;8(1):74–8.
3. Lai CK, Randhawa PS. Cholesterol embolization in renal allografts: a clinicopathologic study of 12 cases. Am J Surg Pathol. 2007;31(4):536–45.
4. Schönermarck U, Guba M, Weiss M, et al. Cholesterol atheroembolic disease in kidney allografts-case report and review of the literature. Clin Nephrol. 2006;66(5):386–90.
5. Berardinell L, Raiteri M, Pasciucco A, et al. The use of a polymeric sealant for prevention of post-transplantation lymphocele. Transplant Proc. 2011;43(4):1072–3.
6. Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR 2012 Annual Data Report. AJ Matas et al. Scientific Registry of Transplant Recipients, Minneapolis Medical Research Foundation, Minneapolis.
7. Guidelines – Nephrol Dial Transplant (2013) 28: ii1–ii71 http://ndt.oxfordjournals.org/.
8. Moers C, et al. Machine perfusion or old storage in deceased-donor kidney transplantation. Machine perfusion versus static cold storage in expanded criteria donor kidney transplantation: 3-year follow-up data. N Engl J Med. 2012;366(8):770–1.
9. Jochmans I, Moers C, Smits JM, et al. Machine perfusion versus cold storage for the preservation of kidneys donated after cardiac death: a multicenter, randomized, controlled trial. Ann Surg. 2010;252(5):756–64.
10. Jochmans I, Moers C, Smits JM, et al. The prognostic value of renal resistance during hypothermic machine perfusion of deceased donor kidneys. Am J Transplant. 2011;11(10):2214–20. Erratum in: Am J Transplant. 2012;12(1):267.
11. Watson CJ, Wells AC, Roberts RJ, et al. Cold machine perfusion versus static cold storage of kidneys donated after cardiac death: a UK multicenter randomized controlled trial. Am J Transplant. 2010;10(9):1991–9.
12. Nicholson ML, Hosgood SA. Renal transplantation after ex vivo normothermic perfusion: the first clinical study. Am J Transplant. 2013;13(5):1246–52.

Live Donor Evaluation

17

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In Italy, in Europe, and in the world, the kidney *transplantation* from a living donor is the main treatment to satisfy the aspiration for a better quality of life of patients with end-stage renal disease.

There are many reasons why the medical physicians (nephrologists, surgeons, etc.) suggest patients and their families taking into consideration the option of kidney donation from living donor instead of applying for the waiting list from deceased donor. The main arguments can be ascribed to two main points:

The transplantation from a *living donor* has better clinical results than the transplantation from deceased donor. This first point is well demonstrated by a recent study [1] that compares the transplantation results of completely HLA-mismatched living and completely HLA-matched deceased. The objective of the study was to evaluate the impact of HLA matching on the outcome of the kidney transplantation. It demonstrated the risk of graft failure increased proportionally with the number of HLA mismatches both in deceased donor and living donor transplantations. At the same time, the relative risk of graft failure for living donor transplantation (even with six mismatches) is the same as for deceased donor transplantation with 0–2 mismatches.

The supply of kidneys from donors with *brain death* is not sufficient to satisfy the claim of kidney transplantation both in the present and in the future. In developed countries (Europe, USA, etc.), there is a constant reduction of donors with brain death. This is not only in the case of brain traumas, but also in the case with

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cerebrovascular accidents typical of the old age. In other words, it is no longer possible to consider the category of "marginal" donors, utilized since more than 20 years, as an unlimited source, but this is a progressively reducing source. This is because of the enhanced health of elderly people thanks to a more appropriate lifestyle and to the widespread use of drugs preventing cerebrovascular diseases.

In some countries (such as Italy, France, Spain, etc.), we observed an organization delay in the management of transplantation from living donors compared to others countries (USA, the Netherlands, UK, Sweden, etc.). This may be caused by the different attitude of doctors in *promoting* living donor transplantation in its several forms: direct donations from related donors, unrelated but family donors, and anonymous samaritan donors and indirect donations (such as crossover or domino).

In those countries where all these options are activated (such as the Netherlands), the number of living donor transplantations is higher than the number of deceased donor transplantations. Roodnat et al. [2] illustrated the successful expansion of the pool of living donor by alternative living donation programs. The reason of this success is due to several factors including an efficient team for the living donor transplantation, the increasing number of potential donors, and the use of alternative programs.

It is essential the role of the living donor transplantation since the preliminary base of the chronic kidney disease (CKD). Starting in the third stage of CKD, awareness and health education in the patients and in their family are very important to promote within the family the practice of living donation. The promptness and effectiveness of this phenomenon allow the preemptive transplantation, which represents the best solution in clinical and social terms. It is also of great *psychological* comfort for the family reaching this goal.

How can we ensure the correct understanding of the donation from living donor at the level of the patient and his/her family? It is important to give a simple and exhaustive response to the sources of doubts and concerns coming from all the actors involved: the receiving patient, the potential donors (better if more than one), the nephrologist, the surgeon, the nurse, the psychologist, etc. There are four main arguments in favor of living kidney transplantation:

1. The *clinical trend* (survival, complications, etc.) in case of living donor transplantation is better than in deceased donor transplantation.
2. The living donor transplantation increases the overall supply of kidney transplant.
3. It is a safe clinical practice for the donor.
4. It gives the opportunity of *preemptive* transplantation.

It is advisable to arrange a presentation to the enlarged family during two or three consecutive meetings. Joint meetings with several family groups with their relatives/patients at the same stage of the disease are of crucial importance. Thanks to such

efforts, the practice of the transplantation from living donor will strengthen in the Southern Europe Countries.

17.1 Evaluation of Living Donor

Several groups of physicians have developed *guidelines* for the evaluation of the living donors. In April 2004, an international consortium of more than 100 leading kidney transplant physicians and surgeons from 40 countries met in Amsterdam to discuss the standard of care for living donors. In partnership with the World Health Organization, this forum proposed a set of standard recommendations for living kidney donor evaluation derived from the best evidence-based medicine. A paper published in *Transplantation* in 2005 provides guidelines for potential kidney donors, but this document does not constitute mandatory regulation. The decision to accept (or not) an individual as a live kidney donor is influenced by medical judgment and physician experience [3].

Other guidelines have been published by several transplant centers from the USA [4] and Europe [5]. These guidelines affirm that before donation, the live kidney donor must receive a complete medical and psychosocial *evaluation*, and they should provide their appropriate, informed, and voluntary consent based on the full understanding of the information generated in the process [3].

Donors should undergo the tests needed to ensure their safety. These include history and physical examination, blood and urine screening tests, cardiovascular screening, and radiographic assessment of the kidneys and vessels and quality of renal functions. Potential donors are evaluated meticulously and repeatedly to confirm excellent general health and bilateral normal renal function.

The standard workup for donor evaluation is summarized in Table 17.1. The section below examines the absolute and relative contraindications and some of the key issues related to the selection and risks for donors. It is important to remember that for all of the issues discussed below, the cutoffs should not be rigidly applied; the potential donor should in fact be evaluated as a whole, and risk associated with a specific medical finding should be assessed in the context of other potential risk factors [6]. The primary responsibility of the donor physicians is to "first, do no harm" and hence to sometimes restrain motivated donors from harming themselves.

17.2 Age

The selection of potential living donor may be determined on the basis of *age* by avoiding, if possible, elderly or minor volunteers. Age <18 years is considered an absolute *contraindication* and most programs consider age of 18–21 years as a relative contraindication [3]. This is because younger donors, even if without risk factors for kidney disease at the time of evaluation, may still develop diabetes, hypertension, and obesity and have more time for these risk factors to progress to

Table 17.1 Evaluation of donor

History and examination	Instrumental investigations	Microbiological screening	Laboratory investigations	Immunological investigations
Family history	Chest radiograph	HBV	Blood count and coagulation	Blood group
Pathological history	Electrocardiogram	HCV	Urea, creatinine, serum uric acid, creatinine clearance, GFR measurement by other methods	Isoagglutinins IgG IgM anti-donor group (if AB0 incompatible)
Physical exam	Echocardiography	HIV	Fasting lipids	HLA typing
Psychiatric history	Stress test	IgG and IgM CMV	Liver function	HLA crossmatch
Medications	Additional cardiac investigations	IgG and IgM EBV	Serum electrolytes	Anti-HLA antibodies
Blood pressure	Renal scintigraphy	Syphilis screening	Fasting blood glucose and/or oral glucose tolerance test	
Cardiovascular disease	Computed tomography	Tuberculosis test	PSA	
BMI	Mammography	IgG and IgM HSV	Urinalysis	
Willingness to donate	Resonance imaging	Urine culture	24 h urine, protein excretion	

BMI body mass index, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *HSV* herpes simplex virus, *GFR* glomerular filtration rate, *PSA* prostate-specific antigen, *HLA* human leukocyte antigen

CKD. *Younger* potential donors with presence of even borderline risk factors are likely at higher long-term risk, and it is recommended to use exclusion criteria more stringently in this population [6].

Old age (defined in various studies as age >60 or 65 years) is not an absolute contraindication to donation. However, in such cases, the medical workup of older donors must be particularly rigorous to ensure that they are suitable for donation [7]. Although older donors are more likely to have complex medical histories and lower glomerular filtration rate (GFR), studies have shown similar outcomes in selected older donors versus younger donors for perioperative outcomes such as operative time, blood loss, and length of hospital stay [8]. With regard to long-term risks, older donors with potential risk factors for kidney disease (such as hypertension) are less likely than younger donors to have enough time for such risk factors to generate kidney disease that would affect their life expectancy [9].

17.3 Hypertension

Donation for some hypertensive individuals may be acceptable if blood pressure is well controlled, the *GFR* for donation and age is as expected, and there are no features of end-organ involvement from *hypertension* [3, 4]. However, the overall risk for cardiovascular events in hypertensive patients is higher than in normotensive individuals with the same age, sex, and race. It is therefore important to perform cardiovascular evaluation and careful blood pressure (BP) measurement in potential living kidney donors with hypertension. The evaluation for hypertension should include BP measurements by experienced providers on three separate occasions; verification of elevated levels should be undertaken with ambulatory BP monitoring. If elevated BP are detected while the potential donor is still under consideration, a cardiovascular (electrocardiogram, echocardiogram, stress test, etc.) and ophthalmologic evaluation should be performed to assess the secondary consequences of hypertension. In addition, a *24-h urine* collection for albumin excretion or a spot urine for albumin/creatinine ratio should be performed along with a urinalysis and a formal GFR measurement. Some patients with easily controlled hypertension who meet other defined criteria (e.g., >50 years of age, GFR >80 ml/min, urinary albumin excretion <30 mg/day) may be considered a low-risk group for development of kidney disease after donation and may be acceptable as kidney donors. Candidates with a blood pressure >140/90 mmHg are generally not accepted as donors. Mild to moderate hypertension that is controlled with single or double antihypertensive agents is not a contraindication to kidney donation providing significant end-organ damage is excluded. The presence of hypertensive end-organ damage, poorly controlled hypertension, and hypertension that requires more than two drugs to achieve adequate control are relative contraindications to living donation [3–5].

17.4 Glomerular Filtration Rate

Among living kidney donors with normal renal function prior to donation, the risk of developing end-stage renal disease (ESRD) after unilateral nephrectomy is not higher than among individuals in the general population [10]. In general, individuals who are being evaluated for kidney donation should have “normal” renal function as determined by *GFR*. Renal function can be measured with various methods, and the multifactorial nature of the various tests may lead to either an overestimation or an underestimation of the true physiological function of the kidneys. However, in the case of living kidney donations, the accurate measure of renal function is of fundamental importance. GFR is either measured as endogenous creatinine clearance by 24-h urine collection or estimated based on serum creatinine measurement by various *formulas* such as Cockroft-Gault, modification of diet in renal disease (MDRD), and the chronic kidney disease epidemiology collaboration equation (CKD-EPI). The use of a 24-h urine collection to estimate GFR with creatinine clearance is the most common technique of donor evaluation; however, creatinine clearance has many deficiencies, including errors from urine

collection. MDRD, CKD-EPI, and other equations based on serum creatinine have been compared with measured GFR, and it was proved that it is unreliable for evaluation of donors; hence, it should be avoided [11]. Likewise, KDIGO guidelines discuss the limitation of these methods especially for patients with normal renal function [12]. The direct measure of GFR using iodinated or radioactive isotopes is ideal for evaluating kidney function in donors. This is because the methods that measure renal function with a higher precision use radioisotopic markers for *scintigraphy* such as technetium-99m-labeled diethylenetriaminepentaacetate (DTPA), chrome-51m-labeled ethylenediaminetetraacetate (EDTA), and techenetium-99m-labeled mercaptoacetyltriglycine (MAG3). In addition to these functional tests, imaging techniques such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are used to determine the vasculature, kidney size, and volume [13].

Although various reports of normal kidney function stratified by age differ somewhat, due to the technique used and the proportion of patients with medical problems that are included, the importance to use different cutoffs depending on the age of the potential donor can be seen from any reports. Several studies recommend that living donors should have a GFR of ≥80 ml/min or, alternatively, a normal kidney function for age and gender [5, 7].

17.5 Diabetes Mellitus

All donors should be evaluated with fasting blood *glucose*. Diabetes is associated with a higher *risk* of postsurgical complications and of future development of renal failure compared to the general population. The individuals at risk of developing type 2 diabetes include those with a familiar history, a body max index (BMI) >30 kg/m^2, woman with gestational diabetes, and excessive alcohol use. Individuals with a history of diabetes or fasting blood glucose ≥126 mg/dl (≥7 mmol/l) on at least two occasions should not donate [3]. Only one study, carried out in Japan, examined the effect of impaired glucose tolerance on living donor outcome. The results of this study suggest that individuals who have glucose intolerance without diabetic complication may be able to donate their kidney safely with little surgical complication and slightly higher morbidity if strict evaluation is performed before transplant [14]. Individuals often lose weight and change their lifestyle (exercise, diet), leading to an improvement of their results and increasing their eligibility as donors. It is therefore important that these modifications of lifestyle and risk factors be sustained after donation occurs.

Dyslipidemia should be included in donor risk assessment along with other risk factors although dyslipidemia alone does not exclude kidney donation. All potential donors should have a health-promoting dialogue with doctors (or another health professional) with the objective of promoting on alcohol and smoking cessation among other risk factors [3].

17.6 Obesity

Patients with BMI >35 kg/m^2 should be discouraged from kidney donation, especially when other comorbid conditions are present. Obesity is associated with proteinuria and hypertension and may lead to ESRD. In the case of obese donors, the operative time and the length of hospital stay are longer, and the risk of peri- and postoperative complication is higher than in patients with *BMI* <30 kg/m^2. Overweight donors should be advised to lose weight before donation, and the potential risks of being overweight should be carefully discussed [3–6].

17.7 Proteinuria

Proteinuria should be considered as an ordinary element of the donor evaluation process. The collection of urine should be repeated and its accuracy checked when the result is outside the normal values. Because *proteinuria* is potentially a sign of renal disease, a potential donor with significant and persistent proteinuria should not be considered. A 24-h urine protein higher than 300 mg/day and a urine albumin/creatinine ratio higher than 30 mg/mmol are contraindications to donation. The significance of microalbuminuria and of a 24-h urine protein of 150–300 mg has not been fully evaluated among living kidney donors. However, because the risk of both chronic kidney disease and cardiovascular morbidity increases progressively with increasing albuminuria, such donors require careful evaluation and counseling about the risks of donation [3, 7].

17.8 Hematuria

Potential donors should be subject to urinalysis at least on two separate occasions; two or more positive tests, including trace positive, should be considered as persistent nonvisible hematuria [7]. Isolated microscopic *hematuria* is present in 5–6 % of the general population, and its prevalence increases with age; persistent microscopic hematuria occurs in 3 % of the general population and is closely linked to pathological findings [15]. Isolated hematuria may be urological (including stones, infection, or tumors) or glomerular. Imaging and cystoscopy address urological causes. For glomerular hematuria a renal biopsy is necessary to distinguish IgA nephropathy, thin basement membrane, Alport syndrome, and other causes of renal disease from normal histology [6]. Glomerular pathology precludes donation with the possible exception of thin basement membrane disease [7]. However, donor evaluation guidelines including the Amsterdam Forum have not identified hematuria as a definite or relative contraindication for kidney donation. A recent study shows that persistent glomerular hematuria is a significant risk for persistent proteinuria and progressive renal dysfunction; therefore, potential donors should be excluded [16].

17.9 Nephrolithiasis

In the case of kidney donation from an individual affected by nephrolithiasis, the risks and risk factors for stone formation in that individual have to be defined. Individuals with more than one stone or who have metabolically active *stone formation* are not suitable for kidney donation. Candidates with genetic predisposition to stone disease, such as cystinuria or hyperoxaluria, also are not suitable. Any *metabolic* abnormalities of hypercalciuria, hyperuricemia, and recurrent urinary tract infections are associated with higher risks for recurrent stone formation. An asymptomatic potential donor with a current single stone is suitable for donation if the individual does not have a high risk of *recurrence*, if the stone is smaller than 1.5 cm, and especially if the stone is potentially removable during transplantation [3]. Seventy-seven percent of US programs accept donors with a history of stones [6]. There are few studies that describe the incidence of the risks and complications of recurring stone disease after live kidney donation. A study published in 2013 assessed the outcomes of 41 donors with nephrolithiasis and their recipients; the authors concluded that the presence of small caliceal stones should not constitute an exclusion criteria: only one donor with nephrolithiasis on preoperative imaging who donated the contralateral kidney had a stone episode during the follow-up period. It can therefore be concluded that the risk of clinical stone recurrence in donors and recipients is low [17]. There is no formal donor registry to monitor these patients over time. Further research on the long-term performance of stone formers who donate a kidney would be needed to evaluate whether stone formers selected in an appropriate manner can be considered suitable for donation [18].

17.10 Inherited Renal Disease

A complete *family history* of kidney disease, especially for the cause of renal failure in a genetically related recipient, is critical to the donor evaluation. For example, a significant family history of diabetic nephropathy is usually a contraindication to donation, especially in the case of a young potential donor. In donors with a family history of polycystic kidney disease, ultrasound or computed tomography is highly sensitive in ruling out cystic disease, especially in those aged >30 years [6]. When the kidney failure in the recipient has hereditary causes, genetic testing should be performed to exclude genetic disease in the potential donor. Most common inherited kidney diseases are rare, so clinical *genetics tests* should be performed during the early stages of the donor evaluation process to assess the likelihood of risk occurrence among other family members [7].

17.11 Malignancy

Kidney donor candidates should be screened for both personal and family histories of malignancy. They should undergo standard age and gender-appropriate screening tests as recommended by national organizations. The risk of *malignancy*

increases with age; hence, it is imperative that older donors are screened to exclude malignancy. The Pap test is recommended for all women, prostate-specific antigen test was recommended for male potential donors older than 50 years, mammogram for women older than 40 years, and colonoscopy for individuals older than 5 years [19]. A prior history of the following malignancies usually excludes live kidney donation: melanoma, testicular cancer, renal cell carcinoma, choriocarcinoma, hematological malignancy, bronchial cancer, breast cancer, and monoclonal gammopathy [3]. A prior history of malignancy usually excludes live kidney donation but may be accepted if the specific cancer is curable and the potential transmission of the cancer can reasonably be excluded (examples include colon cancer Dukes A, nonmelanoma skin cancer, or carcinoma in situ of the cervix). The risks of transmission are not zero, however, and the risks and benefits need to be discussed with the potential donor and recipient. An oncology consultation is also recommended to donor candidates with a history of malignancy during the donor evaluation process [3, 20].

17.12 Cardiovascular and Pulmonary Disease

In potential donors, the cardiac assessment should be based on their medical history, the identification of risk factors, the medical examination, the electrocardiographic findings, and on an exercise or pharmacologic stress test. The purpose of *preoperative* evaluation is to assess the patient's current medical status and generate recommendations concerning the evaluation, management, and risk of cardiac problems over the entire perioperative period. The evaluation should also provide a profile of the clinical risk that may influence short- and long-term cardiac outcomes. The clinical predictors of an increased perioperative cardiovascular risk for noncardiac surgery by the American College of Cardiology/American Heart Association identify three categories: major, intermediate, and minor. These guidelines provide a framework for assessing cardiac risk of noncardiac surgery in a variety of patient and surgical situations. Individuals with myocardial dysfunction or coronary ischemia are at increased risk and should generally not donate [3, 21].

Routine preoperative pulmonary function testing is not necessary for potential live kidney donors, unless there is an associated risk factor such as chronic lung disease that significantly increases the anesthetic risk [3].

17.13 Infection

A potential donor should undergo an *infection* screening to identify potential risks resulting from previous or current infections. Such screening is also needed to assess the risks of transmission of infection to the recipient [7]. The risk of *transmissibility* of disease needs to be deeply analyzed because many forms of infectious disease may be benign in a nonimmunocompromised host; in a transplant recipient undergoing an immunosuppressive regimen, these disease entities might be

detrimental and sometimes fatal. The presence of human immunodeficiency virus is an absolute contraindication to living kidney donation. Active hepatitis B virus and hepatitis C virus infection in the donor are usually contraindications to living donor kidney transplantation; however, donors with no evidence of active viral replication may be considered under some circumstances [7, 20]. Many other serological screens are usually performed as part of donor evaluation: for example, the cytomegalovirus (CMV) and Epstein-Barr virus (EBV) status of the donor and recipient should be established before transplantation. Serological *CMV*-positive donors are not precluded from donation to a CMV-negative recipient. The agent for viral prophylaxis might be more intensive during the initial transplant and might extend for a long time in the recipient to prevent acute infection with CMV [22]. When the donor is *EBV* positive and the recipient is EBV negative, the donor and recipient should be counseled about the risk of developing posttransplant proliferative disorder [3, 7]. There are regions in the world with geographical and endemic infectious diseases. Strongyloidiasis in Asia, Chagas disease in Central and South America, and schistosomiasis and malaria in Africa are examples of infectious diseases that have risks of transmission at the time of transplantation. It is important for potential donors to be screened for these diseases if they live in countries where such diseases are endemic [3]. Active mycobacterium tuberculosis infection is a contraindication for donation because tuberculosis can be transmitted from the live kidney donors to their recipients. Nevertheless, donation from individuals with a past history of pulmonary tuberculosis is acceptable [3, 20]. Asymptomatic bacteriuria should be treated before donation. Unexplained hematuria or pyuria necessitates evaluation for adenovirus, tuberculosis, and cancer. Urinary tuberculosis and cancer are contraindications to donation [3].

17.14 Psychosocial Evaluation

The transplant community agrees that, together with the medical evaluation, the predonation *psychosocial* evaluation is a necessary component of the process that determines whether a person is suitable for donation. However, most guidelines do not provide detailed information on how to ensure the genuine altruistic motivation of the donor, safeguarding voluntary consent and evaluating mental suitability [19]. Available psychosocial criteria for living donor selection seem to have been established based on the opinions and the experiences of various specialized institutes rather than on empirical evidence. In general, it is important that all donor candidates receive a psychosocial assessment to identify any risk factors in living organ donors that may lead to poor outcomes. Likewise, special care should be given to assess the differences in psychosocial problems between the donor and the recipient. It is also important to bear in mind that psychosocial evaluation helps clinicians to identify those individuals who need additional support or therapeutic interventions pre- or postdonation [23].

References

1. Laging M, Kal-van Gestel JA, Haasnoot GW, Claas FH, van de Wetering J, Ijzermans JN, et al. Transplantation results of completely HLA-mismatched living and completely HLA-matched deceased-donor kidneys are comparable. Transplantation. 2014;97(3):330–6.
2. Roodnat J, Kal-van Gestel JA, Zuidema W, van Noord MA, van de Wetering J, IJzermans JN, Weimar W. Successful expansion of the living donor pool by alternative living donation programs. Am J Transplant. 2009;9(9):2150–6.
3. Delmonico F, Council of the Transplantation Society. A report of the Amsterdam forum on the care of the live kidney donor: data and medical guidelines. Transplantation. 2005;79(6 Suppl):S53–66.
4. Bia MJ, Ramos EL, Danovitch GM, Gaston RS, Harmon WE, Leichtman AB, et al. Evaluation of living renal donors. The current practice of US transplant centers. Transplantation. 1995;60(4):322–7.
5. Abramowicz D, Cochat P, Claas FH, Heemann U, Pascual J, Dudley C, et al. European renal 370 best practice guideline on kidney donor and recipient evaluation and perioperative care. 371 Nephrol Dial Transplant. 2014:9 pii: gfu216
6. Kher A, Mandelbrot DA. The living kidney donor evaluation: focus on renal issues. Clin J Am Soc Nephrol. 2012;7(2):366–71.
7. Andrews PA, Burnapp L, Manas D, Bradley JA, Dudley C, British Transplantation Society, Renal Association. Summary of the British Transplantation Society/Renal Association U.K. guidelines for living donor kidney transplantation. Transplantation. 2012;93(7):666–73.
8. Neipp M, Jackobs S, Jaeger M, Schwarz A, Lueck R, Gwinner W, et al. Living kidney donors >60 years of age: is it acceptable for the donor and the recipient? Transpl Int. 2006;19(3): 213–7.
9. Steiner RW. 'Normal for now' or 'at future risk': a double standard for selecting young and older living kidney donors. Am J Transplant. 2010;10(4):737–41.
10. Ibrahim HN, Foley R, Tan L, Rogers T, Bailey RF, Guo H, et al. Long-term consequences of kidney donation. N Engl J Med. 2009;360(5):459–69.
11. Rule AD, Gussak HM, Pond GR, Bergstralh EJ, Stegall MD, Cosio FG, et al. Measured and estimated GFR in healthy potential kidney donors. Am J Kidney Dis. 2004;43(1):112–9.
12. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from kidney disease: improving global outcomes (KDIGO). Kidney Int. 2005;67(6):2089–100.
13. Halleck F, Diederichs G, Koehlitz T, Slowinski T, Engelken F, Liefeldt L, et al. Volume matters: CT-based renal cortex volume measurement in the evaluation of living kidney donors. Transpl Int. 2013;26(12):1208–16.
14. Okamoto M, Suzuki T, Fujiki M, Nobori S, Ushigome H, Sakamoto S, et al. The consequences for live kidney donors with preexisting glucose intolerance without diabetic complication: analysis at a single Japanese center. Transplantation. 2010;89(11):1391–5.
15. Choi SR, Sun IO, Hong YA, Kim HG, Park HS, Chung BH, et al. The role of kidney biopsy to determine donation from prospective kidney donors with asymptomatic urinary abnormalities. Transplant Proc. 2012;44(1):11–3.
16. Kido R, Shibagaki Y, Iwadoh K, Nakajima I, Fuchinoue S, Fujita T, et al. Persistent glomerular hematuria in living kidney donors confers a risk of progressive kidney disease in donors after heminephrectomy. Am J Transplant. 2010;10(7):1597–604.
17. Rizkala E, Coleman S, Tran C, Isac W, Flechner SM, Goldfarb D, et al. Stone disease in living-related renal donors: long-term outcomes for transplant donors and recipients. J Endourol. 2013;27(12):1520–4.
18. Ennis J, Kocherginsky M, Schumm LP, Worcester E, Coe FL, Josephson MA. Trends in kidney donation among kidney stone formers: a survey of US transplant centers. Am J Nephrol. 2009;30(1):12–8.

19. Tong A, Chapman JR, Wong G, de Bruijn J, Craig JC. Screening and follow-up of living kidney donors: a systematic review of clinical practice guidelines. Transplantation. 2011;92(9): 962–72.
20. Caliskan Y, Yildiz A. Evaluation of the medically complex living kidney donor. J Transplant. 2012;2012:450471.
21. American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery), American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society for Vascular Surgery. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary. Anesth Analg. 2008;106(3):685–712.
22. Fishman JA, Doran MT, Volpicelli SA, Cosimi AB, Flood JG, Rubin RH. Dosing of intravenous ganciclovir for the prophylaxis and treatment of cytomegalovirus infection in solid organ transplant recipients. Transplantation. 2000;69(3):389–94.
23. Duerinckx N, Timmerman L, Van Gogh J, van Busschbach J, Ismail SY, Massey EK, Dobbels F, ELPAT Psychological Care for Living Donors and Recipients working group. Predonation psychosocial evaluation of living kidney and liver donor candidates: a systematic literature review. Transpl Int. 2014;27(1):2–18.

Living Donor Nephrectomy

18

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18.1 Introduction

Living kidney donation (LKD) is the best option for end-stage renal disease (ESRD) and is nowadays considered a safe procedure for the donor, subject to a mortality rate lower than 0.03 %.

There are different surgical techniques for living donor nephrectomy, and over the years they have changed according to instrumental and surgical innovations. Less invasive surgical procedures using laparoscopic techniques are advocated to improve the postoperative outcome of the donors (less pain, short hospital stay, and a fast return to work).

The surgical procedure and the strategies for the entire donation process should focus on the principle of not damaging the donors and leaving them with a "better kidney."

The classic surgical approach is transperitoneal, where the nephrectomy is performed using a midline or subcostal incision according to the site. This technique includes all the risks of postoperative complications common to the "open" surgery in the abdomen (visceral injuries, small bowel occlusion, etc.). The extraperitoneal approach is performed with a lumbar incision underneath the 12th rib (the excision

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of the 12th rib is seldom necessary) or above it, and it is important not to open the peritoneum or the pleural space.

The laparoscopic technique may be utilized using either the intraperitoneal or the extraperitoneal approach and applying many variants such as the hand-assisted or robotic-assisted techniques [1–5].

A recent Cochrane review [6] compared the results of open and laparoscopic living donor nephrectomy, and the latter technique showed reduced analgesia use, shorter hospital stay, and faster return to normal physical functioning, while the other postoperative complications were comparable. Open nephrectomy had a shorter operating time and warm ischemia period, but the outcomes of the kidney transplantations were comparable in terms of graft survival and function.

Therefore, the surgical techniques should be based on the local expertise of the surgeons to favor the safety and the satisfactory outcome of the kidney transplantation [7].

18.2 "Open" Nephrectomy

18.2.1 Intra-abdominal Approach

The incision may be midline or subcostal left or right according to the laterality of the kidney to be removed. Actually, we prefer a "mini" laparotomy through the right subcostal incision for right nephrectomy. The incision is close to 12 cm, and it is quite similar to the incision when the "hand"-assisted technique is applied. The retractors are moved according to the stage of the procedure.

We start with the mobilization of the colon to expose the Gerota fascia, and we then isolate the ureter and the gonadal vein. The adipose tissue of the kidney is removed, and the gonadal vessels are followed in order to isolate the renal vein. The renal artery is isolated and the upper part of the kidney detached from the adrenal gland. When the kidney has been completely mobilized and the renal vein and artery isolated for up to 3–4 cm, we cut the ureter and place a single vascular clamp for the artery and the vein, which are resected. The kidney is removed and the vein is sutured with 4-0 or 5-0 Prolene, while the artery is sutured with 5-0 Prolene and ligated with 2-0 Vicryl. A drain is left in place and removed on postoperative day 2–3.

In the case of right nephrectomy, we often place a Satinsky clamp at the confluence of the right renal vein to the vena cava, in order to have the vein as long as possible. In the case of a short vessel, we sometimes use a cryopreserved graft from a cadaveric donor (Fig. 18.1).

18.2.2 Retroperitoneal

The donor is placed in the lateral decubitus position on the opposite side of the nephrectomy. The lower leg is bent under the straight upper leg from which it is separated by a pillow. The operating table can be broken under the flank of the donor in

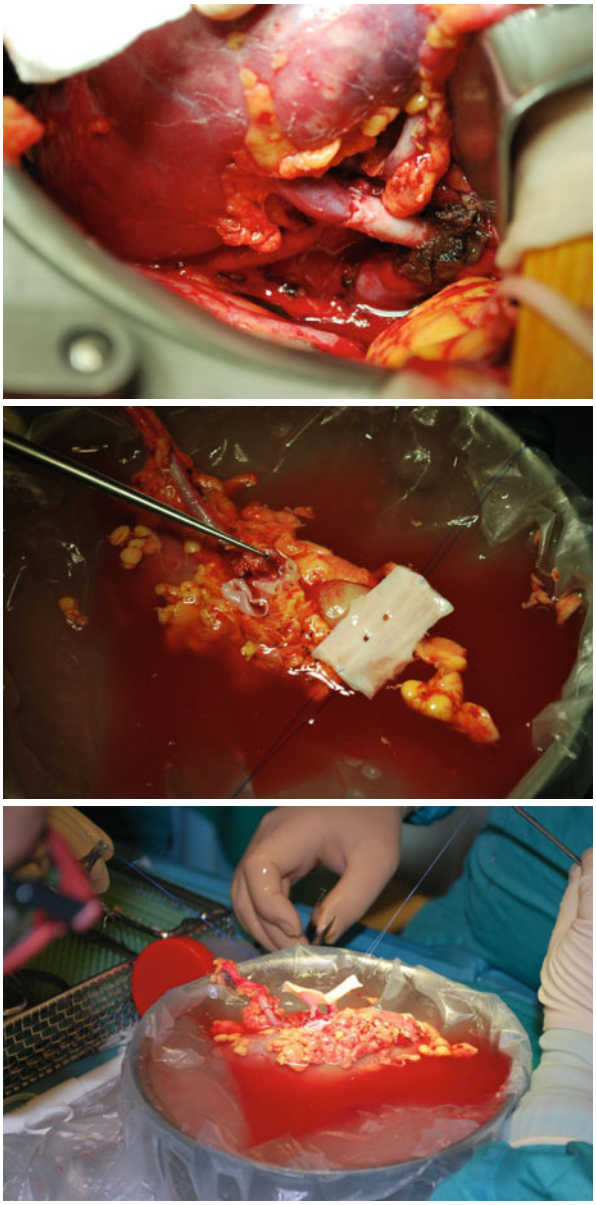

Fig. 18.1 Vein graft for living kidney transplantation and back table of an artery graft for living kidney transplantation

order to open the space between the ribs and the iliac crest and improve the exposure. The incision is performed underneath the 12th rib, which is preserved, following the superior border of the rib toward the umbilicus. During the incision it is important to avoid opening the pleural space. If this complication should occur, it is sufficient to close the hole after aspiration of air and avoid pleural derangement in the postoperative course. The steps of the procedure are the same as with "open" nephrectomy with the exception of the colon mobilization, which is not necessary. The risk of visceral injury is reduced since the peritoneum is left intact. The incision may be a "mini" laparotomy close to 12 cm like the open approach. The additional steps are the isolation of the ureter, the gonadal vein, the renal vein, and the renal artery and the complete removal of the adipose tissue from the kidney. After the complete mobilization of the kidney and 3–4 cm of the renal vein and artery, the ureter is sectioned, a vascular clamp is placed for the vein and the artery, and the kidney is removed. The vein and the artery are sutured as previously described.

18.3 Laparoscopic Nephrectomy

18.3.1 Intra-abdominal

The donor is placed in a full flank position, on the opposite site with respect to the procured kidney; during the operation, the operating table should be flexed so that the hyperextension of the flank elevates the kidney for a better exposure. The lower leg is bent, and three pillows support the upper leg. After creation of the pneumoperitoneum (12–15 mm water), the camera is introduced through the umbilical port. Three ports are mandatory and are the following: a 12-mm umbilical port for the camera, a 12-mm port between the umbilicus and the anterior iliac spine homolateral to the side of the nephrectomy, and a 5-mm port 3 cm lateral to the umbilicus and 3 cm below the costal border. An additional 5-mm port may be used for retraction and placed on the anterior axillary line. First the surgeon incises the lateral peritoneal reflection from the splenic or hepatic flexure to the pelvic inlet and dissects the Gerota fascia from the colonic mesentery. The surgeon then mobilizes the spleen (for left nephrectomy) or the liver and duodenum through kocherization (for right nephrectomy). The gonadal and adrenal veins are sutured, and the upper pole of the kidney is separated from the donor adrenal gland. When preparing the hilum, the lumbar veins are ligated to fully mobilize the renal vein, and the arterial vein can then be dissected. For right nephrectomy, some authors suggest performing interaortocaval space dissection in order to ligate the renal artery at its origin from the aorta. The lower pole of the kidney can then be dissected and separated from the posterior attachments. The ureter is clipped at the level of the iliac vessels and dissected together with the periureteral fatty tissue. If the retrieval is performed through an endobag, it should be placed within the abdominal cavity and around the kidney before the vessel is sectioned. The sequential ligation of the renal artery and vein is then performed with a GI vascular stapler, which should be oriented in a plane parallel to the inferior cava vein. In right nephrectomy, the surgeon may want to use a

TA stapler which only fires two staple lines, leaving the surgeon the option of cutting the vessel open at the time of retrieval and gaining extra length for the anastomoses on the recipient. Otherwise, a Satinsky clamp can be used to obtain a cuff of cava vein, which is then sutured. The kidney is finally retrieved through either the extension of one of the incisions or through a Pfannenstiel incision [8].

18.3.2 Retroperitoneal

The donor is placed in a flank position. The incision is performed below the tip of the 12th rib, at the angle of the 12th rib and the lateral margin of the iliocostal muscle. The retroperitoneal space is reached after sectioning the thoracolumbar fascia and then expanded through a balloon device, which is then replaced by a 12-mm camera port. A 10-mm port is placed between the iliac crest and the 12th rib on the axillary line. A 5-mm port is inserted 5 cm above the anterior spine of the iliac bone. The pneumoperitoneum is created with a pressure of 5–10 mmHg. The kidney and ureter are dissected retroperitoneally; the renal artery and vein are identified from the posterior side and separated from the perivascular lymphatic and fatty tissue, after dissecting and sectioning the lumbar, gonadal, and adrenal veins. The perinephric fat and the fibrous capsule are then dissected, and the kidney is totally isolated from the adrenal gland and surrounding structures. The ureter is then sectioned at about 20 cm from the hilum. A 5-cm Pfannenstiel incision is then performed and an anterior vesical space created by finger dissection connected to the retroperitoneal space. A LapDisc is placed in the Pfannenstiel incision to maintain the pneumoretroperitoneum, through which an endobag is introduced in order to retrieve the graft. The renal artery and vein are then sectioned through a vascular staple. Finally the graft is removed through the Pfannenstiel incision. For right nephrectomy, the retroperitoneoscopic approach allows better access to the hilum and a good length of both artery and vein. This approach also allows the use of a Satinsky clamp to gain extra length for the right renal vein [9].

18.3.3 Hand-Assisted

The hand-assisted procedure has been described both for the transperitoneal [10] and for the retroperitoneoscopic approaches [11]. The position of the patient on the operating table and the number and sites of the ports are similar to those described above for the pure retroperitoneoscopic and transperitoneal laparoscopic approach. The difference is mainly due to the site of the larger incision for the introduction of the operating hand.

For the retroperitoneoscopic technique, the surgeon performs a Pfannenstiel incision through which the preperitoneal space is created through blunt manual dissection. Using a hand-assisted device (LapDisc, HandPort, Omniport), the surgeon introduces his left hand between the abdominal wall and the peritoneum, and then all the other ports can be placed. For the transperitoneal approach, the HandPort is placed through the periumbilical incision extended for 7 cm.

The introduction of the hand facilitates the process of vascular exposure, shortens the cold ischemia time because the graft can be easily removed, and increases donor safety. In the case of sudden bleeding, the surgeon can immediately clamp the vessel with the fingers while the assistant performs the laparotomy, reducing the blood loss.

18.3.4 Robotic

The donor is placed on the operating table in the lateral decubitus position (opposite to the side of the nephrectomy). The table is then flexed in order to open the angle between the costal margin and the anterior iliac crest. In the case of hand assistance, the incision for the HandPort is performed infraumbilically on the midline for an extension of approximately 7 cm; a Pfannenstiel incision is performed for the graft extraction in the case of pure robotic technique. The ports are then placed in the left lateral wall and inguinal region (12 mm) and in the subxiphoid lower lateral abdomen (8 mm). The da Vinci robot is brought to the operating table, and the arms are connected to the trocars; the surgeon operates from a remote console, which controls the movements of the articulated robotic arms mimicking the human hand. The surgical steps are similar to transperitoneal laparoscopic nephrectomy [12, 13].

18.3.5 Notes

A few reports describe the utilization of natural orifices for the extraction of the graft, in order to maximize the cosmetic result. In particular, the transvaginal access has been the most widely employed. The robotic platform is needed for this procedure. The patient is placed in a lateral decubitus position with the legs abducted and the superior hip externally rotated. A SILS (single-incision laparoscopic surgery) port is introduced through a 4-cm intraumbilical incision, and one 12-mm as well as two 5-mm trocars are inserted. After achieving the pneumoperitoneum, the vaginal port is positioned through a 2.5-cm transverse incision at the vaginal apex. After dissecting the rectum from the posterior vaginal wall, the peritoneum is opened and a bariatric 12-mm port is inserted. The following surgical steps are similar to what was previously described for robotic and laparoscopic surgery. The endobag is necessary for this procedure; before the vascular sectioning, the kidney is placed in the endobag and the bag closed excluding the hilum. After stapling the renal artery and vein, the kidney is delivered through the vaginal access [14].

18.4 Donor Risk and Complications

A review of the literature regarding the outcome of open donor nephrectomy (ODN) compared to laparoscopic donor nephrectomy (LDN) shows that LDN provides less postoperative pain, a shorter hospital stay, and a faster recovery. However, when

complications occur they can be life-threatening and lead to reoperation [15]. Although the mortality for kidney donors is very low, around 0.03 % mainly due to hemorrhage and pulmonary embolism, the overall complication rate approaches 10 %, with major intraoperative bleeding and conversion to laparotomy occurring, respectively, in 1.6 % and 13 % of cases [16].

Pure laparoscopic and hand-assisted laparoscopic donor nephrectomy (HALDN) are the most widely adopted surgical techniques for living donor nephrectomy. While the pure laparoscopic technique is preferred by experienced laparoscopic surgeons, HALDN presents a shorter learning curve and offers a sort of bridging procedure from the open technique to a pure laparoscopic approach [17]. The only real disadvantages of HALDN are the higher costs due to the HandPort where there is also an increased risk of incisional hernia. The retroperitoneal approach has the undeniable advantage of decreasing postoperative ileus and generally reduces the postoperative course, but the narrow working space makes the technique a real challenge even for experienced laparoscopic surgeons [18]. As confirmed by a recent randomized controlled trial, the outcome in terms of donor safety and length of hospital stay did not differ significantly between the group of donors who underwent retroperitoneoscopic surgery and those who underwent intraperitoneal laparoscopy.

The technical surgical characteristics should also be taken into consideration when deciding the best approach. The left kidney is always the best option when the two organs are equal in terms of function; in the case of vascular anomaly for the left kidney, it is the surgeon's responsibility to decide which kidney to procure. Although the laparoscopic procedure has been preferentially adopted on left grafts because of an easier anatomical condition, no real contraindication exists for the procurement of right grafts since the posttransplant outcome of the grafts appears to be equal for either side [19, 20].

The main issue, however, is to preserve any possible arterial branch, especially when they appear to perfuse the lower pole of the kidney, in order to avoid ureteral ischemia. In experienced centers, the outcomes of grafts with multiple arteries are comparable to those with a single artery as regards early and late vascular and urologic complications and graft function. In a transplant center, any possible anatomical variant can be corrected at the bench surgery through vascular reconstruction, maybe employing vascular grafts, often avoiding multiple anastomoses in the recipient [21].

The economic aspect also has an important role in the choice of surgical technique. The economic advantage leans toward the open technique because the cost of the laparoscopic tools and of the possible complications exceeds the benefit due to the reduced hospital stay and the faster return to work activity [22].

In conclusion, no clear superiority of one technique over the others has been shown so far. The surgeon's preference is still the main discriminating factor. The principles to be followed are: ensure the best outcome for the donor and make the best use of the available grafts. This last rule means not refusing donors on the basis of purely anatomical difficulties and providing the best outcome of the graft after transplantation, saving possible multiple arteries and adopting reconstructive

techniques. Although laparoscopic donor nephrectomy is the standard procedure nowadays, it is still perfectly acceptable to use the open technique if the laparoscopic approach is not feasible or puts the graft at risk of failure due to some anatomical variances.

References

1. Ratner LE, Ciseck LJ, Moore RG, et al. Laparoscopic live donor nephrectomy. Transplantation. 1995;60:1047–9.
2. Wolf Jr JS, Tchetgen MB, Merion RM. Hand-assisted laparoscopic live donor nephrectomy. Urology. 1998;52:885–7.
3. Gill IS, Rassweiler JJ. Retroperitoneoscopic renal surgery: our approach. Urology. 1999;54:734–8.
4. Wadstrom J, Lindstrom P. Hand-assisted retroperitoneoscopic living donor nephrectomy; initial 10 cases. Transplantation. 2002;73:1839–40.
5. Matas AJ, Bartlett ST, Leichtman AB, Delmonico FL. Morbidity and mortality after living kidney donation, 1999–2001: survey of United States transplant centers. Am J Transplant. 2003;3:830–4.
6. Wilson CH, Sanni A, Rix DA, Soomro NA. Laparoscopic versus open nephrectomy for live kidney donors. Cochrane Database Syst Rev. 2011 Nov 9;(11):CD006124. doi: 10.1002/14651858.CD006124.pub2.
7. Nephrol Dial Transplant. European Renal Best Practice Transplantation Guideline Development Group. 2013;28: ii1–71 doi: 10.1093/ndt/gft218 http://ndt.oxfordjournals.org/ at Oxford Journals on 4 Oct 2013.
8. Minnee RC, Idu MM. Laparoscopic donor nephrectomy. Neth J Med. 2010;68(5):199–206.
9. Tanabe K, Miyamoto N, Ishida H, et al. Retroperitoneoscopic live donor nephrectomy (RPLDN): establishment and initial experience of RPLDN at a single center. Am J Transplant. 2005;5:739.
10. Maartense S, Idu M, Bemelman FJ, Balm R, Surachno S, Bemelman WA. Hand-assisted laparoscopic live donor nephrectomy. Br J Surg. 2004;91(3):344–8.
11. Wadstrom J. Hand-assisted retroperitoneoscopic live donor nephrectomy: experience from the first 75 consecutive cases. Transplantation. 2005;80:1060.
12. Horgan S, Benedetti E, Moser F. Robotically assisted donor nephrectomy for kidney transplantation. Am J Surg. 2004;188(4A Suppl):45S–51.
13. Giacomoni A, Di Sandro S, Lauterio A, et al. Evolution of robotic nephrectomy for living donation: from hand-assisted to totally robotic technique. Int J Med Robot. 2014;10(3):286–93.
14. Kaouk JH, Khalifeh A, Laydner H, et al. Transvaginal hybrid natural orifice transluminal surgery robotic donor nephrectomy: first clinical application. Urology. 2012;80(6):1171–5.
15. Fonouni H, Mehrabi A, Golriz M, et al. Comparison of the laparoscopic versus open live donor nephrectomy: an overview of surgical complications and outcome. Langenbecks. 2014;399(5):543–51.
16. Banga N, Nicol D. Techniques in laparoscopic donor nephrectomy. BJU Int. 2012;110(9):1368–73.
17. Dols LF, Kok NF, d'Ancona FC, et al. Randomized controlled trial comparing hand-assisted retroperitoneoscopic versus standard laparoscopic donor nephrectomy. Transplantation. 2014;97(2):161–7.
18. Liu N, Wazir R, Wang J, Wang KJ. Maximizing the donor pool: left versus right laparoscopic live donor nephrectomy-systematic review and meta-analysis. Int Urol Nephrol. 2014;46(8):1511–9.

19. Omoto K, Nozaki T, Inui M, et al. Impact of right-sided nephrectomy on long-term outcomes in retroperitoneoscopic live donor nephrectomy at single center. J Transplant. 2013;2013: 546373.
20. Chedid MF, Muthu C, Nyberg SL, et al. Living donor kidney transplantation using laparoscopically procured multiple renal artery kidneys and right kidneys. J Am Coll Surg. 2013;217(1):144–52.
21. Hamidi V, Andersen MH, Oyen O, et al. Cost effectiveness of open versus laparoscopic living-donor nephrectomy. Transplantation. 2009;87(6):831–8.
22. Florian TF. Laparoscopic living donor nephrectomy: making optimal use of donors without doing harm. Transplantation 2014;15;98(11):1144.

Renal Transplantation: Surgical Technique

19

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19.1 Standard Technique

19.1.1 Side Positioning of the Kidney

Results of kidney transplantation have dramatically improved during the past three decades due to refinements in surgical instruments, new immunosuppressive regimens, improved kidney preservation, and advances in antimicrobial therapy [1–4]. However, the principles of the vascular anastomosis technique proposed by Carrel in 1902 and the accomplishment of the implantation in the iliac vessels by Kuss in 1951 are still in use [5–7].

It has been suggested that the left kidney is easier to transplant than the right kidney because of the longer length of the left renal vein, facilitating the formation of the venous anastomosis [8–10]. Registry reports of kidneys transplanted from the late 1980s to the early 1990s suggested that early deceased donor allograft survival was superior with left-sided kidneys [11, 12]. United Network for Organ Sharing (UNOS) data on transplants between 1988 and 1991 [11] showed 3-month allograft survival rates of 90.4 % in recipients of left-sided kidneys versus 85.0 % in recipients of right-sided kidneys ($P = 0.0005$). This effect appeared to be lost with longer follow-up, and beyond 1 year there was no effect seen in either report. Early allograft survival in this era has greatly improved compared with that reported in the above studies, with 1-year graft survival being over 90 % [13]. More recently, a study from an Australian center suggested no effect on deceased donor allograft outcome between left and right kidneys [14]. A European study from Dublin [15]

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demonstrated no effect on delayed graft function or long-term allograft survival between recipients of left and right kidney transplants. Moreover, renal function, as measured by serum creatinine, was similar in the two groups considering a direct comparison of right and left kidneys from the same donor to be a more accurate method which would account for other donor variables, such as donor age, gender, cause of donor death, and comorbidities.

However, the left renal vein has additional properties which can present challenges for the transplant surgeon. These include anatomical variations of the posterior tributaries [16] and the presence of pre- and retroaortic veins [17] and of a double left renal vein [18]. These anomalies may negate any preexisting advantage attained using the left kidney with its longer renal vein.

19.1.2 Graft Renal Vein Anastomosis

During renal transplantation the standard vein anastomosis technique is an end-to-side anastomosis performed between the graft renal vein and the recipient's external iliac vein with an extraperitoneal approach over the iliopsoas muscle, after skin incision in the right or left hypogastric fossa, sectioning the muscular plane, and isolation and double ligation of the epigastric vessels (Fig. 19.1).

Anastomosis was performed using 6-0 Prolene running stitches in the end-to-side fashion (Fig. 19.2).

In cases of external iliac vein thrombosis, the common iliac vein can be useful to perform the anastomosis, and only in rare cases is the inferior vena cava of the recipients anastomosed with the graft renal vein with an intraperitoneal approach.

A short or damaged right renal vein (SRRV) can make renal transplantation very difficult [19–22]. The right renal hilum has a single long artery and a short vein that causes difficulties while performing a venous anastomosis either from a living or cadaveric kidney and especially when the right renal artery has an aortic patch in the

Fig. 19.1 Extraperitoneal approach to external iliac vessels: left eternal iliac vein encircled with blue Silastic rubber; left external iliac artery encircled with red Silastic rubber

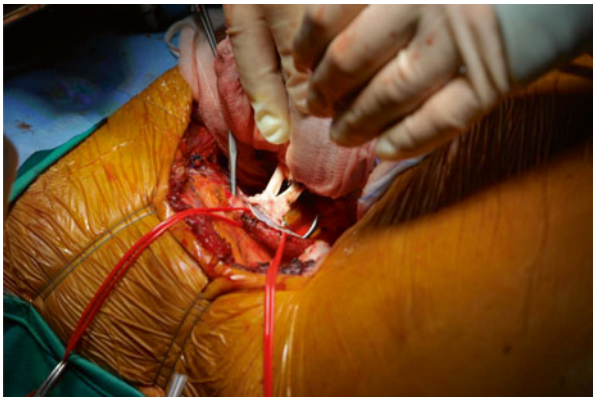

Fig. 19.2 Graft renal vein anastomosis with recipient's external iliac vein clamped

case of a cadaveric donor. It is more complicated and takes more time to perform the transplant especially with either deep iliac vessels or in obese patients. Anastomosis of an SRRV to the common or external iliac vein has been reported to be associated with technical problems such as angulation or tension of the venous anastomosis, reduced mobility, limited placement and inspection of the graft for hemostasis, and possible kinking of the donor artery. One technical solution consists of a more extensive mobilization of the recipient's vessels, with the increased risk of lymphocele formation. A number of surgical approaches have been described to solve the problem of an SRRV [21]. Several techniques have been used to overcome this technical challenge, such as renal vein extension using an autologous saphenous graft, bovine arterial heterograft, or polytetrafluoroethylene (PTFE) vascular prostheses [21–24]. A technique of extending the right renal vein using the contiguous inferior vena cava was introduced to make vascular anastomosis feasible [25–27]. Using this technique, a portion of the contiguous inferior vena cava is removed during organ harvesting to extend very short right renal veins from cadaveric kidneys [27]. The technique for obtaining an appropriate length of the right renal vein using the vena cava is simple, physiological, and feasible and does not interfere with multiorgan procurement [19–27].

Short vessels can take up more time and extend the length of the warm ischemia during renal vessel anastomoses. In renal transplantation, when the vein is slightly longer than the corresponding artery, it allows easier venous and arterial anastomoses. Renal vein thrombosis is a serious complication leading to graft nephrectomy in many cases, despite medical or surgical therapy [21, 22]. In addition to this risk, there is concern that continuous thrombosis to the recipient vein may lead to a pulmonary embolus [21, 26, 27]. Right renal vein elongation with the inferior vena cava seems to be a much better approach than a venous saphenous autograft; spiral gonadal veins, bovine arterial heterografts, and vascular prostheses have also been used for these surgical challenges [21–24].

Dissection of the hilum of the donor kidney to lengthen the right renal vein is not recommended due to the risk of parenchyma hemorrhage and injury of the blood

supply of the pelvis and ureter and can consequently cause necrosis to both. Faulty surgical techniques may be the cause for the majority of late ureteral stenosis due to ureteral devascularization and ischemia [19]. Right renal vein extension is particularly important in kidneys with multiple vessels, in order to avoid lesions to these venous and arterial variations, and to ensure easier anastomosis and possibly better positioning of the kidney. There is no increased risk with the use of the vena cava extension, and we recommend that the donor team routinely provide the right kidney with the vena cava attached. This allows the recipient team to determine whether an extension is appropriate for the particular recipient. This technique eliminates the need to mobilize the recipient's vessels by a more extensive dissection, and the internal iliac vein division is not required. The kidney graft can easily be placed above the iliac vessels. This technique also preserves a patch of cadaveric aortic wall along with the right renal artery, thereby minimizing the risk of arterial graft kinking, renal transplant artery stenosis, and thrombosis.

Performance of this technique depends upon the vena cava being left intact and attached to the right renal vein when the organs are separated [25, 27]. Multiple right renal veins can also be elongated with the inferior vena cava.

19.1.3 Graft Renal Artery Anastomosis

There are few data available comparing vascular anastomosis techniques, and while there is no difference in the incidence of renal artery stenosis following end-to-end (hypogastric artery) or end-to-side (common or external iliac artery) arterial anastomosis, most of the data come from retrospective studies [28]. A recent prospective study by Matheus et al. [29] showed similar short and long results with both arterial anastomosis techniques. Although some doubts persist about what the best technique for arterial anastomosis is, end-to-side anastomosis to the external iliac artery is the preferred technique in deceased donors, because of the large Carrel patch obtained from the aorta [30]. Due to similar postoperative results in both arterial anastomosis groups, the choice of anastomosis technique in cadaver grafts still depends on surgical circumstances such as arteriosclerosis involving internal or external iliac arteries, multiple renal arteries, kidney position, and surgical team preferences [31, 32]. All the surgical procedures were performed by unilateral extraperitoneal approach to the iliac vessels. Anastomosis was performed using 7-0 Prolene running stitches in the end-to-side fashion (Fig. 19.3).

However, some authors described the possibility of the occurrence of erectile dysfunction and renal artery stenosis with end-to-end internal iliac artery anastomosis [33, 34]. Arterial stenosis is a challenging issue, with a high incidence of complications during arterial stenosis correction, either by surgery or by stent insertion using percutaneous methods, due to the angle of the arterial anastomosis point [28]. Arterial anastomosis to the external iliac artery could reduce the incidence of erectile dysfunction, mainly in cases of a second transplant, in which the first kidney graft had been anastomosed to the contralateral internal iliac artery [31, 32, 35].

Fig. 19.3 Graft renal artery anastomosis with recipient's external iliac artery clamped superiorly and inferiorly and sectioned with an aortic punch

19.1.4 Graft Ureteral Anastomosis with the Recipient's Bladder

In 1954, Muray et al. [36] performed the first successful renal transplant between identical twins using a Politano-Leadbetter (PL) intravesical technique to reimplant the transplanted ureter [37]. The PL technique [37] was subsequently used by most centers in North America owing to its high success rate in correcting vesicoureteral reflux in children. One source of complications with the PL technique was the cystostomy itself, with the risk of postoperative urine leakage. As a result, many centers began to use an anterior extravesical ureteral anastomosis. The extravesical ureteroneocystostomy was first described by Witzel in 1896 [38] and was popularized by Lich et al. [39]. Herein called the Lich-Gregoir, it is characterized by extravesicular access, the formation of an antireflux tunnel, and an urothelial anastomosis. An incision is made in the bladder wall musculature at the dome for 2–3 cm to expose the mucosa of the bladder wall. The mucosa of the bladder is then continuously sutured to the ureteral end with absorbable sutures (5-0 polydioxanone). The detrusor muscle is then closed over the anastomosis to create a submucosal tunnel approximately 2–3 cm long using 4-0 nonabsorbable polypropylene suture. Several operative techniques for reimplantation of the transplant ureter into the bladder have been used successfully. The anterior, extravesical approach described by Lich and associates [39] has been widely used, as has the Politano-Leadbetter intravesical technique [37]. Modifications of these methods have been described [40]. Each of these methods has advantages but also drawbacks; the Lich-Gregoir (LG) technique saves time but is not particularly effective in preventing reflux; the Politano-Leadbetter approach effectively prevents reflux but requires more difficult exposure and a longer operating time. The LG technique significantly lowers the risk of ureteral leakage when compared with the PL technique and significantly lowers the risk of hematuria when compared with the PL technique in kidney transplantation.

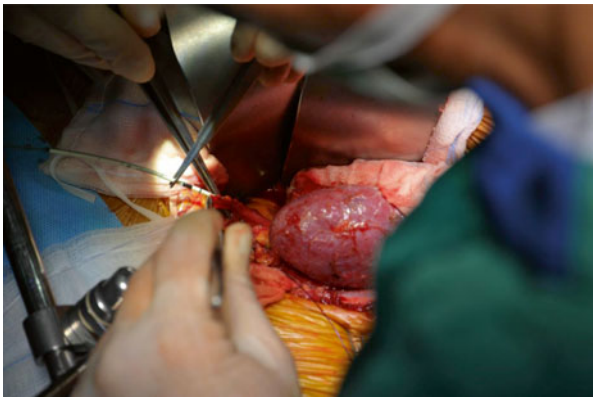

Fig. 19.4 Donor kidney ureteral anastomosis with the recipient's bladder: ureteral stenting with double J stent 6–12 French

There were no differences in the prevalence of ureteral strictures and vesicoureteral reflux between the various techniques [41]. The higher risk of urinary leakage in the PL group might be the result of the second cystotomy, which creates a potential extra leakage site. It has also been hypothesized that the use of a shorter segment of the ureter in the LG technique decreases the risk of distal ureteral necrosis and therefore results in a lower risk of urine leakage at the ureterovesical junction [42, 43]. The higher rate of hematuria in the PL group might also be explained by the extra cystotomy, from which bleeding can arise. The Lich-Gregoir and Politano-Leadbetter approaches are used either with or without a temporary ureteral stent; however, ureteral stenting seems to have a significant protective effect against the development of urological complications after renal transplantation, as described in a meta-analysis by Mangus et al. and a Cochrane review by Wilson et al. [44, 45] (Fig. 19.4).

However, whether ureteral stenting is preferably performed by routine or selective approach in the case of problematic anastomoses has still to be clarified [46–48]. Some studies have shown an increase in urinary tract infections (UTIs) with ureteral stenting [45, 49–51]. Wilson et al. describe a relative risk of 1.49 (95 % CI 1.04–2.15) for UTIs with ureteral stenting, unless the patients were given prophylactic antibiotics, in which case the prevalence was equal to the non-stented group (RR 0.97, 95 % CI 0.71–1.33) [45]. There were not enough data in the included studies to assess the effect of ureteral stenting on UTIs.

19.2 Double Kidney Transplantation with "Suboptimal" Donors

The shortage of kidney donors is a rate-limiting step in renal transplantation programs in many transplant centers. To overcome the disparity between supply and demand of organs, various strategies such as the increased use of organs from extended criteria donors (ECD) have been proposed. Double kidney transplantation

(DKT) is another approach for expansion of the existing deceased donor pool. The number of functioning nephrons is the most important determinant of kidney function; therefore, the higher number of functioning nephrons supplied by dual marginal kidneys should slow down or even prevent progressive deterioration of graft function [52]. Transplantation of two marginal kidneys rather than one suboptimal kidney to one recipient would result in more functioning nephrons that ultimately may improve the patient and graft outcome [52]. The decision to perform DKT is based on gross characteristics of the kidneys and results of the renal biopsy. Small kidneys or those with extensive surface scarring or cystic lesions are discarded. In addition to the clinical evaluation of the donor, the selection criteria of deceased donor (DD) kidneys are based on a macroscopic and histological assessment. Marginal DD kidneys are classified as low or high risk, based on the donor's age, renal function, and comorbidities; in particular, high-risk marginal kidneys are considered those from donors aged >70 years or 60–69 years with at least two of the following conditions: serum creatinine >1.5 mg/dL, calculated creatinine clearance <60 ml/min, history of hypertension or diabetes, proteinuria >1 g/day, and cause of death is cerebrovascular. High-risk donors are subjected to a renal biopsy, and, based on the Karpinski [53] and Remuzzi [52] histological scores, the kidneys are allocated for single kidney transplantation (SKT) or DKT. Using a histological scoring system (4–18), a score between 0 and 12 is attributed to the kidneys, depending on the percentage of glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arterial and arteriolar narrowing. Kidneys scoring 0–3 are used for SKT, those scoring 4–6 are used for DKT, and those scoring >6 are considered inadequate for transplantation. Recipients are required to sign an informed consent form for DKT before placement on the waiting list. Potential recipients of DKT (mainly older than 60 years) are also placed on an additional, but separate, DKT waiting list, which facilitates the allocation of ECD kidneys in an "old-for-old" fashion, i.e., kidneys from older donors are allocated to older recipients. Patients are considered suitable for DKT listing when they satisfy the standard criteria for eligibility for kidney transplantation, but are excluded if highly sensitized (PRA >50 %) or if undergoing retransplantation, because allocation of DKT is not based on HLA-matching. In addition, patients affected by polycystic kidney disease are excluded unless they have been nephrectomized or clearly have enough space in the iliac fossa for the implantation of two kidneys. DKT is considered contraindicated in the presence of severe bilateral atherosclerosis of the iliac vessels. The first DKT from an adult deceased donor was reported in 1996 by Johnson et al. [54]. The classic surgical technique for DKT included bilateral placement of the two kidneys extraperitoneally through two separate Gibson incisions or intraperitoneally through a midline incision. Unilateral DKT was first reported by Masson et al. in 1998 [55]. There are various surgical techniques for unilateral DKT [56–58]. Ekser et al. proposed sequential DKT: one kidney with its vessels anastomosed end-to-side to recipient vessels (external iliac artery and vein) and then another kidney with its vessels anastomosed to the external iliac artery and vein distal to the site of the first anastomosis [59]. After creating an adequate extraperitoneal space, the right donor kidney is preferably placed superiorly because its renal vein can be lengthened by a segment of inferior vena cava. Another reason to position the right kidney

superolaterally in the right flank is because the right kidney has a longer artery. If necessary, the internal iliac (hypogastric) vein is dissected to mobilize the external iliac vein and thus facilitate renal vein anastomoses to the external iliac vein of the recipient. After revascularization of the right kidney, vascular clamps are placed immediately below the venous and arterial anastomoses. The left donor kidney is transplanted distally, allowing the transplanted right kidney to continue to be perfused. Extravesical ureteroneocystostomies are performed separately, according to the Lich-Gregoir technique, with a double J stent for each ureter, leaving the ureter of the upper transplanted kidney lateral to the lower one. Veroux et al. proposed another technique for DKT. They joined the arteries and veins of the two kidneys at bench surgery. The newly joined artery and vein of the two kidneys were then anastomosed end-to-side to the common iliac artery and external iliac vein, respectively [60]. Although unilateral DKT is a complex surgical procedure, it can reduce the cold ischemia time and the operating time, leaving the contralateral side intact for further transplant. On the other hand, kidneys with multiple arteries and veins can be transplanted like a single kidney.

References

1. Ali-El-Dein B, Osman Y, Shokeir AA, Shehab El-Dein AB, Sheashaa H, Ghoneim MA. Multiple arteries in live donor renal transplantation: surgical aspects and outcomes. J Urol. 2003;169:2013–7.
2. Schnuelle P, Lorenz D, Trede M, Van Der Woude FJ. Impact of renal cadaveric transplantation on survival in end-stage renal failure: evidence for reduced mortality risk compared with hemodialysis during long-term follow-up. J Am Soc Nephrol. 1998;9:2135–41.
3. Simmons RG, Abress L. Quality-of-life issues for end-stage renal disease patients. Am J Kidney Dis. 1990;15:201–8.
4. Barry JM. Current status of renal transplantation. Patient evaluations and outcomes. Urol Clin North Am. 2001;28:677–86.
5. Moore FD. Transplantation–a perspective. Transplant Proc. 1980;12:539–50.
6. Carrel A, Guthrie CC. Anastomosis of blood vessels by the patching method and transplantation of the kidney. 1906 [classical article]. Yale J Biol Med. 2001;7:243–7.
7. Cinqualbre J, Kahan BD. René Küss: fifty years of retroperitoneal placement of renal transplants. Transplant Proc. 2002;34:3019–25.
8. Mandal AK, Cohen C, Montgomery RA, Kavoussi LR, Ratner LE. Should the indications for laparoscopic live donor nephrectomy of the right kidney be the same as for the open procedure? Anomalous left renal vasculature is not a contraindication to laparoscopic left donor nephrectomy. Transplantation. 2001;71(5):660–4.
9. Satyapal KS, Kalideen JM, Singh B, Haffejee AA, Robbs JV. Why we use the donor left kidney in live related transplantation. S Afr J Surg. 2003;41(1):24–6.
10. Buell JF, Abreu SC, Hanaway MJ, et al. Right donor nephrectomy: a comparison of hand-assisted transperitoneal and retroperitoneal laparoscopic approaches. Transplantation. 2004;77(4):521–5.
11. Gjertson DW. Multifactorial analysis of renal transplants reported to the United Network for Organ Sharing Registry. Clin Transpl. 1992;35:299–317.
12. Feduska NJ Jr, Cecka JM. Donor factors. Clin Transpl. 1994;12:381–94.
13. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. N Engl J Med. 2000;342(9):605–12.

14. Johnson DW, Mudge DW, Kaisar MO, et al. Deceased donor renal transplantation–does side matter? Nephrol Dial Transplant. 2006;21(9):2583–8.
15. Phelan PJ, Shields W, O'Kelly P, et al. Left versus right donor deceased renal allograft outcome. Transpl Int. 2009;22(12):1159–63.
16. Satyapal KS, Kalideen JM, Haffejee AA, Singh B, Robbs JV. Left renal vein variations. Surg Radiol Anat. 1999;21(1):77–81.
17. Raheem OA, O'Brien M, Glacken P, Mohan P, Hickey DP. A review of the anatomical variations of the posterior tributaries of the left renal vein. Ir J Med Sci. 2008;177(1):59–62.
18. Toda R, Iguro Y, Moriyama Y, Hisashi Y, Masuda H, Sakata R. Double left renal vein associated with abdominal aortic aneurysm. Ann Thorac Cardiovasc Surg. 2001;7(2):113–5.
19. Jordan ML, Cook GT, Cardella CJ. Ten years of experience with vascular complications in renal transplantation. J Urol. 1982;128:689–92.
20. Salaman JR, Clarke AG, Crosby DL. The management of kidney transplants damaged during their removal from the donor. Br J Urol. 1974;46:173–7.
21. Janschek EC, Rothe AU, Holzenbein TJ, Langer F, Brugger PC, Pokorny H, et al. Anatomic basis of right renal vein extension for cadaveric kidney transplantation. Urology. 2004;63:660–4.
22. Nerstrom B, Ladefoged J, Lund F. Vascular complications in 155 consecutive kidney transplantations. Scand J Urol Nephrol. 1972;6 Suppl 15:65–74.
23. Santiago-Delpin EA, Gonzalez Z. Successful renal vein reconstruction with a polytetrafluoroethylene vascular graft in kidney transplantation. Am J Surg. 1985;149:310–1.
24. Spees Jr EK, Oakes DD, Light JA, Perloff LJ, Reckard CR. Successful renal vein reconstruction with bovine arterial heterografts. Ann Surg. 1977;186:749–51.
25. Taylor RJ, Hakala TR, Rosenthal JT. Use of vena cava to extend the right renal vein in cadaveric transplants. Surg Gynecol Obstet. 1985;160:279–80.
26. Szmidt J, Frunze S, Karolak M, Madej K, Sablinski T, Nazarewski S. Right renal vein extension technique inhuman kidney transplantation. Eur Urol. 1989;16(3):204–6.
27. Chopin DK, Popov Z, Abbou CC, Auvert JM. Use of vena cava to obtain additional length for the right renal vein during transplantation of cadaveric kidneys. J Urol. 1989;141:1143–4.
28. Sutherland RS, Spees EK, Jones JW, Fink DW. Renal artery stenosis after renal transplantation: the impact of the hypogastric artery anastomosis. J Urol. 1993;149:980–5.
29. Matheus W, Reis LO, Ferreira U, et al. Kidney transplant anastomosis internal or external iliac arteries? Urol J. 2009;6:260–6.
30. Ersöz S, Anadol E, Aydintuğ S, Bumin C, Erkek B, Ateş K. Anastomotic artery stenosis in living related kidney transplantation: the impact of anastomotic technique. Transplant Proc. 1996;28:2331–2.
31. Bitker MO, Benoit G. Surgical aspects of kidney transplantation in France in 1997. Eur Urol. 1998;34:1–5.
32. Moon I, Kim Y, Park J, Kim S, Koh Y. Various vascular procedures in kidney transplantations. Transplant Proc. 1998;30:3006.
33. Abdel-Hamid IA, Eraky I, Fouda MA, Mansour OE. Role of penile vascular insufficiency in erectile dysfunction in renal transplant recipients. Int J Impot Res. 2002;14:32–7.
34. Prieto Castro RM, Anglada Curado FJ, Regueiro López JC, et al. Treatment with sildenafil citrate in renal transplant patients with erectile dysfunction. BJU Int. 2001;88:241–3.
35. Moray G, Bilgin N, Karakayali H, Haberal M. Comparison of outcome in renal transplant recipients with respect to arterial anastomosis: the internal versus the external iliac artery. Transplant Proc. 1999;31:2839–40.
36. Murray JE, Merrill JP, Harrison JH. Renal homotransplantations in identical twins. 1955. J Am Soc Nephrol. 2001;12(1):201–4.
37. Politano VA, Leadbetter WF. An operative technique for the correction of vesicoureteral reflux. J Urol. 1958;79(6):932–41.
38. Witzel O. Extraperitonealeureterocystostomie mit Schrag-kanalbildung. Zentralbl Gynakol. 1986;11:289.
39. Lich R, Hoverton LW, Davis LA. Recurrent urosepsis in children. J Urol. 1961;86:554.

40. Schanfield I. New experimental methods for implantation of the ureter in bladder and conduit. Transplant Proc. 1972;4:637–8.
41. Alberts VP, Idu MM, Legemate DA, et al. Ureterovesical anastomosis technique in kidney transplantation: a systematic review and meta-analysis. Transpl Int. 2014;27:593–605.
42. Masahiko H, Kazunari T, Tokumoto T, Ishikawa N, Yagisawa T, Toma H. Comparative study of urosurgical complications in renal transplantation: intravesical versus extravesical ureterocystoneostomy. Transplant Proc. 2000;32:1844–6.
43. Kayler L, Kang D, Molmenti E, Howard R. Kidney transplant ureteroneocystostomy techniques and complications: review of the literature. Transplant Proc. 2010;42:1413–20.
44. Mangus RS, Haag BW. Stented versus nonstented extravesical ureteroneocystostomy in renal transplantation: a meta-analysis. Am J Transplant. 2004;4:1889–96.
45. Wilson CH, Bhatti AA, Rix DA, Manas DM. Routine intraoperative ureteric stenting for kidney transplant recipients. Cochrane Database Syst Rev. 2005;(4): CD004925.
46. Georgiev P, Boni C, Dahm F, et al. Routine stenting reduces urologic complications as compared with stenting "on demand" in adult kidney transplantation. Urology. 2007;70:893–7.
47. Dominguez J, Clase CM, Mahalati K, et al. Is routine ureteric stenting needed in kidney transplantation? A randomized trial. Transplantation. 2000;27:597–601.
48. Osman Y, Ali-El-Dein B, Shokeir AA, Kamal M, El-Din AB. Routine insertion of ureteral stent in live-donor renal transplantation: is it worthwhile? Urology. 2005;65:867–71.
49. Lee JR, Bang H, Dadhania D, et al. Independent risk factors for urinary tract infection and for subsequent bacteremia or acute cellular rejection: a single-center report of 1166 kidney allograft recipients. Transplantation. 2013;96:732–8.
50. Akoh JA, Rana T. Effect of ureteric stents on urological infection and graft function following renal transplantation. World J Transplant. 2013;3:1–6.
51. Fayek SA, Keenan J, Haririan A, et al. Ureteral stents are associated with reduced risk of ureteral complications after kidney transplantation: a large single center experience. Transplantation. 2012;93:304–8.
52. Remuzzi G, Grinyo J, Ruggenenti P, et al. Early experience with dual kidney transplantation in adults using expanded donor criteria. J Am Soc Nephrol. 1999;10:2591–8.
53. Karpinski J, Lajoie G, Cattran D, et al. Outcome of kidney transplantation from high-risk donors is determined by both structure and function. Transplantation. 1999;67:1162–7.
54. Johnson LB, Kno PC, Defoe DC, et al. Double adult renal allograft: a technique for expansion of the cadaveric kidney donor pool. Surgery. 1996;12:580–4.
55. Masson D, Hefty T. A technique for the transplantation of 2 adult cadaver kidney grafts into 1 recipient. J Urol. 1998;160:1779–80.
56. Vroux M, Corona D, Gagliano M, et al. Monolateral dual kidney transplantation from marginal donors. Transplant Proc. 2007;39:1800–2.
57. Gaber O, Shokouh-Amiri H, Nezakatgoo N, et al. Jpsi lateral placement in double-kidney transplantation. Transplantation. 2007;84:929–31.
58. Haider HH, Jllanes HG, Ciancio G, et al. Dual kidney transplantation using midline extraperitoneal approach: description of a technique. Transplant Proc. 2007;39:1118–9.
59. Ekser B, Furian L, Broggiato A, et al. Technical aspects of unilateral dual kidney transplantation from expanded criteria donors: experience of 100 patients. Am J Transplant. 2010; 10:1–8.
60. Veroux P, Giuffrida G, Cappellani A, et al. Two-as-one monolateral dual kidney transplantation. Urology. 2011;77:227–30.

The Intraoperative and Perioperative Management of Kidney Transplantation

20

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20.1 Introduction

Each year about 160–170 individuals per million habitants need dialysis treatment due to the loss of the renal function. Renal transplant is, in this context, the treatment of choice for most patients affected by renal insufficiency.

Kidney transplant is thus an effective treatment for renal disease that generally allows for a quantity and quality of life that is significantly superior to that offered by dialysis [1, 4].

Kidney transplant is a successfull treatment for patients with chronic renal failure and around 80 % of the kidneys are perfectly functioning, for the continuous improvement of the immunosuppressive therapies, thus involving ever larger bands of the population [2–4].

In this perspective there is also an increase in the age of the transplantees that today is close to 55 years [5]. These conditions associated to an improved survival with dialysis support have determined an increase in the number of patients on the waiting list who, in the kidney transplant, takes on significant proportions, so that it has been necessary to try to increase the supply in order to deal with the growing demand.

For this end, different strategic lines have been becoming popular, which we shall just list here:

- Improvments in ex vivo kidney perfusion and in surgical technique, especially with the development of the double kidney transplant, have permitted the use of kidneys once discarded due to their biopsy score.

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- There are also pathways dedicated to promoting the donation of a kidney from a living donor, as there are programmes relating to organ donation from donors whose hearts have stopped beating.

For these topics we should refer to the chapter relating to organ donation.

20.2 Candidate Selection

Preoperative multispecialist assessment takes on primary importance in determining the best clinical approach vis-à-vis the patients to be submitted to this particular procedure. The anaesthesiological examination [9], increasingly addressed to recognising and managing the risk factors instead of the exclusion of the critical patients, represents a focal point for the realisation of the therapeutic programme and is functional to obtaining all the information that allow us to correctly position the patient to be submitted to any important surgery, especially in the transplant field [9, 10]; thus, the anaesthesiological/intensive management in these cases requires a precise preoperative assessment:

- Clinical impact and pharmacological interrelations with the chronic home therapies [11]
- Good knowledge and control of the significant variations in the turnover of liquids, electrolytes and volaemia of the underlying kidney disease
- Optimisation of any comorbidities to minimise the risks of morbidity and mortality during the perioperative period [7, 9, 12]

The main comorbidities to be taken into consideration are those relating to the haemodynamic situation that, as regards the pressure profile, may present two distinct pictures:

- A situation relating to hard-to-control hypertension, often treated with pharmacological combinations
- A tendency to hypotension that in some cases can make tolerance to haemodialysis difficult

It is worth remembering that coronary disease is the main cause of death in the kidney transplant patient.

In this light a cardiological assessment of the candidates is required; a Cochrane meta-analysis indicates a good reliability to the echo-cardiovascular stress test with dobutamine [13] even if it underlines that no test can provide the certain exclusion of cardiovascular events [14].

To add to the preoperative evaluation relating to the cardiorespiratory study, we should investigate some specific characteristics that concern kidney transplant and that may be less well known.

Starting from the trophic status, a basal condition correlated to obesity seems to be non-influential in that it does not significantly modify the survival of the patient and of the graft; not only that, but an abundant muscular endowment correlated with high levels of creatinaemia seems to favourably affect the posttransplant prognosis [15]. On the opposite side, low levels of albuminaemia and a lack of nutritional intake are related to cardiovascular complications, graft failure and delayed graft function also increases in these patients [16]. As regards the pre-transplant haemodialysis treatment, they do not seem to significantly affect the general outcome: in particular the blood purification modality between continuous haemofiltration and intermittent dialysis does not seem to be influential [17]. There is some evidence on a lowering in the mortality levels in patients on peritoneal dialysis treatment without differences in the functional recovery of the graft and its duration [18]. Another observation concerns the time spent on haemodialysis before the transplant; even in this case there is no significant difference related to this factor [19]. On the contrary, the presence of high levels of phosphataemia seems to be significantly related to worse outcome; the optimisation of the control of the phosphates in dialysis patients can significantly improve prognosis [20]. As regards the kidney transplant in diabetic patients, a good pre-transplant glycaemic control seems fundamental for patient's survival, whereas it does not seem that even a poor control affects the short-term functionality [21]. Another aspect concerns the response of the haemodialysis patient awaiting transplant submitted to therapy with erythropoietin: it has been demonstrated that the failed or poor response to treatment is significantly correlated to a worse prognosis [22].

None of these additional factors can hamper the execution of the transplant; however, their impact on the results cannot be ignored.

20.2.1 Anaesthesiological Procedures

As can be easily imagined, there is currently no recognised anaesthesiological protocol available worldwide to determine a clear preference for one technique or the other; indeed, all the various anaesthetic techniques have been tested without detecting a preferential treatment [23, 24].

The choice of technique to be used is in any case subjective, but there are effective interventions that can improve the results. The first point that should be underlined is that relating to the pharmacological choice. There are no particular strategies that have demonstrated a superiority in the management of narcosis. In particular, there is no adverse evidence vis-à-vis the use of volatile anaesthetics. Numerous studies have shown the use of sevoflurane without adverse side effects, believed to be potentially nephrotoxic in experimental animal studies. That effect has never been observed in man [25].

The anaesthesiological procedure provides for the use of a series of drugs such as hypnotics, opioids, myorelaxants, halogenated vapours and local anaesthetics; hereunder we shall analyse some drugs used of these families; we shall also evaluate

the appropriateness of the use of vasopressors in haemodynamic support for patients submitted to kidney transplant from cadaver.

20.2.1.1 Hypnotics

The half-life of these drugs and their metabolites are increased in the presence of renal dysfunction [26, 27].

20.2.1.2 Opioid Analgesics

A build-up of morphine-6-glycuronide has been shown in patients with ESKD, so caution is required in the use of morphine, while *fentanyl and its derivates* (sufentanil, remifentanil, etc.) seem to be the safest drugs to be used during the surgical operation for kidney transplant [26, 27].

20.2.1.3 FANS

The inhibition of prostaglandin synthesis (for cyclooxygenase inhibition) by this pharmacological class, under some conditions, can cause a vasoconstriction of the kidney's arterioles determining an alteration in renal function.

Gastrointestinal disorders, alteration of platelet function and allergic reactions are not infrequent complications.

20.2.1.4 Myorelaxants

Vecuronium: 20 % to 30 % is eliminated with the urine; so a risk of accumulation is possible at subsequent doses.

Atracurium and derivates: these are recommended in that they are degraded via the Hofmann reaction (esterase hydrolysis independent of renal function), although eliminated by the renal pathway states of prolonged muscular relaxation have not been evidenced [28].

Rocuronium: the data collected suggest that in patients affected by ESKD, the extrarenal clearance of rocuronium allows for a scarce accumulation; indeed the unmodified elimination through the bile is around 80 % [29].

20.2.1.5 Halogenates

All of them undergo a biotransformation; however, chronic renal insufficiency does not modify their action, as their effect on the CNS depends on pulmonary elimination [25, 30].

20.2.2 Local Anaesthetics

20.2.2.1 Aminoamides

Lidocaine, mepivacaine, bupivacaine, levobupivacaine, and ropivacaine

The amide anaesthetics are degraded less rapidly and are catabolised almost exclusively by hepatic microsomes, increasing stability and duration [32, 33].

20.2.2.2 Vasopressors

Dopamine: there is a large amount of literature that shows harmful effects for renal function [34, 35]. Hence, the use of dopamine, to support graft perfusion during the renal transplant, cannot be recommended.

Dobutamine: positive inotrope of choice in patients with low cardiac ejection fraction, to be used with advanced monitoring.

Terlipressin: there are no described experiences, if not for its use in maintaining satisfactory tissue perfusion values in donors who are often nonresponders to classical catecholamines [36]; in fact the increase in mean arterial pressure could lead to an increase in the renal perfusion with a reduction in the sympathetic nervous system activity and that of the rennin-angiotensin-aldosterone system.

The reduction of this vasoconstriction activity induces a reduction in the renal vascular resistances determining the increase of the renal plasma flow and thus of the glomerular filtrate.

Adrenaline/noradrenalin: On the grounds of the current data, owing to the potential damage induced by the relative renal vasoconstriction, there are no definite recommendations regarding the use of these drugs; nevertheless, their use seems reasonable in order to avoid hypotensive episodes, in particular after reperfusion.

Following these considerations, the most appropriate anaesthesiological conduct seems to be:

- *Induction*
  - Propophol 1.5–2 mg/kg
  - Fentanyl 0.7–1.5 γ/kg or its derivates (remifentanil, sufentanil at equivalent dosages)
  - Atracurium 0.5 mg/kg
  - Halogenates of the latest generation vaporised with a mix of air and oxygen. Administration of immunological therapy laid down by a nephrological colleague
  - Antibiotic prophylaxis for 24 h (ampicillin/sulbactam 3 g × 2/day)
- *Maintenance*
  - Fentanyl drip 50–100 γ/h or its derivates at equivalent dosage
  - Halogenated vapours with a mix of air and oxygen and maintenance MAC
  - Atracurium supplementary doses of 0.1–0.2 mg/kg (TOF)

In actual fact, the intraoperative pharmacological management of general anaesthesia does not seem to be the key problem; there are no drugs relating to narcosis whose use significantly increases risk in the intra- and postoperative phase. What appear to be the major concerns involve the management of the hydro-electrolyte balance, the haemodynamic control and the correction of acidosis typical of the patient affected by chronic renal insufficiency.

A precondition that warrants careful evaluation and that involves the management of the intraoperative anaesthesiological therapeutic programme is that relating to the pre-transplant dialysis session.

It is certainly an error to perform an over-subtractive dialysis with the result of taking a hypovolaemic patient to operation; this should be appropriately reintegrated in the intraoperative phase to foster the graft perfusion and to stimulate the recovery of diuresis.

At the same time preoperative dialysis is essential to correct possible and relatively common pictures of hypervolaemia and hyperpotassaemia observable in patients affected by ESKD.

If we exclude the transplants from live donor that can benefit from an accurate preoperative preparation, the time that elapses between the availability of an organ from cadaver donor and its attribution to the opportune recipient is too short to allow for an accurate study of the overall situation.

For this purpose it is fundamental to have an accurate intraoperative monitoring that provides for:

- PAM personalised values for a good peripheral tissue perfusion
- HR possible alterations of the rhythm due to electrolytic disorders [37]
- PVC maintain values from 8 to 10 mmHg [9]
- EGA control of Hb and acid-base balance
- SNG also useful for the kalaemic control (resins of polystyrene sulphonate)
- TOF (train-of-four) for the qualitative neuromuscular monitoring
- Bladder catheter
- Probe for the control of central temperature

For many years there has been an international debate on the fact that central venous pressure can be the most adequate instrument for evaluating the refilling status; however, for this purpose it is being used by most centres that deal with kidney transplant.

Another problem is to obtain an invasive arterial monitoring that is not always possible when the patient has been submitted to different accesses for arteriovenous fistulae. If the access has been limited to one limb, then the contralateral radial artery can be incannulated.

The arm bearing the arterial-venous fistula must be carefully protected.

Integration with other haemodynamic data allows for reliable information; even if following a further technological evolution, the use of a transoesophageal ultrasound could provide more accurate information.

Key Intraoperative Points

Gastroprotection.

Hydration (crystalloids from 7.5 to 15 ml/kg/h) [35, 38].

For possible volaemic replacement (blood/plasma), the use of colloids is more debateable: albumin seems to have a favourable impact on the outcome

even if this fact is not universally shared [39]; among the plasma expanders the gelatines appear to be preferable [40].
Hyperglycaemia correction [21].
Maintenance of the acid-base balance [41].
Administration of methylprednisolone before graft reperfusion.
Diuretic (mannitol 0.5–1 g/K in 15/20′ before reperfusion) [42–44].
Infiltration of the surgical wound with local anaesthetic [42, 43].

At the end of the surgical operation, the patient will be admitted to postoperative intensive therapy where, apart from a reawakening assisted by general anaesthesia, the best therapeutic continuity will be assured to safeguard the hydro-electrolytic and volemic homeostasis by means of the continuous monitoring of the clinical, biohumoral, immunological and inflammatory parameters that allow us to set up the most adequate therapy to foster the graft's perfusion and functional recovery.

20.2.3 Postoperative Intensive Therapy

Patients who required after transplant more than 36 hours in the ICU, have a far worse clionical outcome if compared to other patients [45].

There are many aspects concerning the postoperative management of the patients with renal transplant, but the ones reported are the strengths to be optimised for graft perfusion [31]:

- Nephrotoxic substances must be avoided.
- It is necessary to optimise the hydro-electrolyte therapy.
- Very careful volemic recovery.
- Good analgesia; patient pain with compromised renal function can be an important problem that requires cautious therapy.
- Control and stabilisation of the immunosuppressive therapy.

Hence, the therapeutic support ought to deal with:

- Rapid respiratory weaning
- Echo Doppler control of the graft vascularisation
- Pressure control with special attention to hypotension episodes

A certain number of patients present a hard-to-control hypertension that, present in the preoperative analysis, maintains its characteristics even after the transplant and requires an intensive treatment:

Electrolyte control (laboratory/blood gas analyser in the ward)
Attention to the various schemes of immunosuppressive therapy
Analgesia in drip with fentanyl 0.8 – 1 γ/kg/h or its derivates for ~3 h [9, 46]
Analgesia induction with tramadol (300 max 400 mg/day)

The diuresis behaviour in the postoperative phase can be extremely varied: an important polyuria can appear with a scarce purification effect that must be followed with a careful reintegration of the fluid losses; vice versa there can be a persistent anuria at times masked in patients who presented perioperative residual diuresis.

In any case it is necessary to be alerted in the eventuality of an initial graft dysfunction:

Diuretic (furosemide in drip 250/500 mg/day) [42–44, 47]
Possible hydro-electrolytic and volemic replacement [25, 31, 45, 48]
Transfer from POIC (postoperative intensive care) to the ward within 24 h [45]

The main critical points in the postoperative management of the kidney transplantee, in order of importance, seem to be:

Delayed graft function that seems to be related to graft failure and mortality [49, 50]. The aetiology of this manifestation is complex and ranges from the organ's quality, the ischaemia times and the hydro-electrolytic and haemodynamic intraoperative management.
The immunosuppressive situation can also be responsible [51].
Postoperative hypertension control can determine a worse prognosis for the transplanted kidney and for the general outcome. The best therapeutic strategy seems to be treatment with ACE inhibitors that result to be more effective in haemodynamic stabilisation [51, 52].
Hyperglycaemia, even a new onset posttransplant. For a few patients, strict control seems to be fundamental for graft survival [21, 53, 54], while for others control can tolerate higher glycaemia levels with no problems.

References

1. Pham P-T, Pham P-A, Pham P-C, Parikh S, Danovitch G. Evaluation of adult kidney transplant candidates. Semin Dial. 2010;23(6):595–605.
2. Hourmant M, Garandeau C. The evolution of kidney transplantation over the last 20 years. Presse Med. 2011;40(11):1074–80.
3. Petrović D, Mijailović Z, Popovska B, Canović P. Assessment of patient eligibility for kidney transplant procedure. Med Glas Ljek Komore Zenicko-Doboj Kantona. 2012;9(2):174–9.
4. Neipp M, Jackobs S, Klempnauer J. Renal transplantation today. Langenbecks Arch Surg. 2009;394:1–16.
5. Centro Riferimento Trapianti Emilia-Romagna. Attività di donazione e trapianto di organi, tessuti e cellule. Resoconto. 2011.

6. Diaz G, O'Connor M. Cardiovascular and renal complications in patients receiving a solid-organ transplant. Curr Opin Crit Care. 2011;17:382–9.
7. Potluri K M.D., Hou S M.D. Obesity in kidney transplant recipients and candidates. Am J Kidney Dis. 2010;56(1):143–56.
8. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing committee to revise the 2002 guidelines on perioperative cardiovascular evaluation for noncardiac surgery) – developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery Anesthesia & analgesia. 106(3):2002.
9. Niemann CU, Eilers H. Abdominal organ transplantation. Minerva Anestesiol. 2010;76(4):266–75. Epub 2009 Nov 24.
10. Gowdak LHW, de Paula FJ, et al. Screening for significant coronary artery disease in high-risk renal transplant candidates. Coron Artery Dis. 2007;18(7):553–8.
11. Boerner BP, Shivaswamy V, Desouza CV, Larsen JL. Diabetes and cardiovascular disease following kidney transplantation. Curr Diabetes Rev. 2011;7(4):221–34.
12. Pilmore H, Dent H, Chang S, McDonald SP, Chadban SJ. Reduction in cardiovascular death after kidney transplantation. Transplantation. 2010;89:851–7.
13. Wang LW, Fahim MA. Hayen A. Mitchell RL, Baines L, Lord S, Craig JC, Webster AC. Cardiac testing for coronary artery disease in potential kidney transplant recipients. Cochrane Database Syst Rev. 2011;10(12):200–215:CD008691.
14. Wang LW, Fahim MA, Hayen A, Mitchell RL, Lord SW, Baines LA, Craig JC, Webster AC. Cardiac testing for coronary artery disease in potential kidney transplant recipients: a systematic review of test accuracy studies. Am J Kidney Dis. 2011;57(3):476–87.
15. Streja E, Molnar MZ, Kovesdy CP, Bunnapradist S, Jing J, Nissenson AR, Mucsi I, Danovitch GM, Kalantar-Zadeh K. Associations of pretransplant weight and muscle mass with mortality in renal transplant recipients. Clin J Am Soc Nephrol. 2011;6(6):1463–73. doi:10.2215/CJN.09131010. Epub 2011 Mar 17.
16. Molnar MZ, Kovesdy CP, Bunnapradist S, Streja E, Mehrotra R, Krishnan M, Nissenson AR, Kalantar-Zadeh K. Associations of pretransplant serum albumin with post-transplant outcomes in kidney transplant recipients. Am J Transplant. 2011;11(5):1006–15.
17. Wang AY, Ninomiya T, Al-Kahwa A, Perkovic V, Gallagher MP, Hawley C, Jardine MJ. Effect of hemodiafiltration or hemofiltration compared with hemodialysis on mortality and cardiovascular disease in chronic kidney failure: a systematic review and meta-analysis of randomized trials. Am J Kidney Dis. 2014;63(6):968–78.
18. Molnar MZ, Mehrotra R, Duong U, Bunnapradist S, Lukowsky LR, Krishnan M, Kovesdy CP, Kalantar-Zadeh K. Dialysis modality and outcomes in kidney transplant recipients. Clin J Am Soc Nephrol. 2012;7(2):332–41.
19. Kohei N, Sawada Y, Hirai T, Omoto K, Ishida H, Tanabe K. Influence of dialysis duration on the outcome of living kidney transplantation. Ther Apher Dial. 2014;18:481.
20. Sapir-Pichhadze R, Parmar K, Kim SJ. Pretransplant serum phosphate levels and outcomes after kidney transplantation. J Nephrol. 2012;25(6):1091–7.
21. Molnar MZ, Huang E, Hoshino J, Krishnan M, Nissenson AR, Kovesdy CP, Kalantar-Zadeh K. Diabetes association of pretransplant glycemic control with posttransplant outcomes in diabetic kidney transplant recipients. Care. 2011;34(12):2536–41.
22. Costa NA, Kshirsagar AV, Wang L, Detwiler RK, Brookhart MA. Pretransplantation erythropoiesis-stimulating agent hyporesponsiveness is associated with increased kidney allograft failure and mortality. Transplantation. 2013;96(9):807–13.
23. Dauru M, et al. Combined general and epidural anesthesia with ropivacaine for renal transplantation. Minerva Anestesiol. 2003;69:873–84.

24. Nicholls AJ, Tucker V, Gibbs P. Awake renal transplantation; a realistic alternative to general anesthesia. Transplant Proc. 2010;42:1677–8.
25. Schmid S, Jungwirth B. Anaesthesia for renal transplant surgery: an update. Eur J Anaesthesiol. 2012;29:552–8.
26. Niscola P, et al. The use of major analgesics in patients with renal dysfunction. Curr Drug Targets. 2010;11(6):752–8.
27. Murphy EJ. Acute pain management pharmacology for the patient with concurrent renal or hepatic disease. Anaesth Intensive Care. 2005;33(3):311–22.
28. Fahey MR, Rupp SM, Fisher DM, et al. The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. Anesthesiology. 1984;61:699–702.
29. Cooper RA, Maddineni VR, Mirakhur RK, et al. Time course of neuromuscular effects and pharmacokinetics of rocuronium bromide(Org 9426) during isoflurane anaesthesia in patients with and without renal failure. Br J Anaesth. 1993;71:222–6.
30. Teixeira S, Costa G, Costa F, da Silva VJ, Mota A. Sevoflurane versus isoflurane: does it matter in renal transplantation? Transplant Proc. 2007;39(8):2486–8.
31. Guay J. The benefits of adding epidural analgesia to general anesthesia: a metaanalysis. J Anesth. 2006;20:335–40.
32. Hansen TG. Ropivacaine: a pharmacological review. Expert Rev Neurother. 2004;4(5): 781–91.
33. Foster RH, Markham A. Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. Drugs. 2000;59(3):551–79.
34. Venkataraman R. Can we prevent acute kidney injury? Crit Care Med. 2008;36:S166–71.
35. Tang IY, Murray PT. Prevention of perioperative acute renal failure: what works? Best Pract Res Clin Anaesthesiol. 2004;18(1):91–111.
36. Blasco V, Leone M, et al. Impact of terlipressin on renal graft function. Shock. 2008;29(6):667Y669.
37. Catherine M. A randomized, double-blind comparison of Lactated Ringer's solution and 0.9% NaCl during renal transplantation. Anesth Analg. 2005;100:1518–24.
38. De Gasperi A, Narcisi S, Mazza E, Bettinelli L, Pavani M, Perrone L, Grugni C, Corti A. Perioperative fluid management in kidney transplantation: is volume overload still mandatory for graft function? Transplant Proc. 2006;38(3):807–9.
39. Dawidson IJ, Sandor ZF, Coorpender L, et al. Intraoperative albumin administration affects the outcome of cadaver renal transplantation. Transplantation. 1992;53:774–82.
40. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367(20):1901–11.
41. Tiggeler RG, Berden JH, Hoitsma AJ, Koene RA. Prevention of acute tubular necrosis in cadaveric kidney transplantation by the combined use of mannitol and moderate hydration. Ann Surg. 1985;201:246–51.
42. Weimar W, Geerlings W, Bijnen AB, Obertop H, van Urk H, Lameijer LD, Wolff ED, Jeekel J. A controlled study on the effect of mannitol on immediate renal function after cadaver donor kidney transplantation. Transplantation. 1983;35(1):99–101.
43. Hanif F, Macrae AN, Littlejohn MG, Clancy MJ, Murio E. Outcome of renal transplantation with and without intra-operative diuretics. Int J Surg. 2011;9(6):460–3.
44. Cantarovich F, Rangoonwala B, Lorenz H, Verho M, Esnault VL. High-dose furosemide in acute renal failure study group. High-dose furosemide for established ARF: a prospective, randomized, double-blind, placebo-controlled, multicenter trial. Am J Kidney Dis. 2004;44(3):402–9.
45. Klouche K, Amigues L, Massanet P, Garrigue V, Delmas S, Szwarc I, Beraud JJ, Mourad G. Outcome of renal transplant recipients admitted to an intensive care unit: a 10-year cohort study. Transplantation. 2009;87(6):889–95.
46. Upton RN, Semple TJ, Macintyre PE. Pharmacokinetic optimisation of opioid treatment in acute pain therapy. Clin Pharmacokinet. 1997;33(3):225–44.

47. Shilliday IR, Quinn KJ, Allison MEM. Loop diuretics in the management of acute renal failure:a prospective, double-blind, placebo-controlled, randomized study. Nephrol Dial Transplant. 1997;12:2592–6.
48. Hadimioglu N, et al. The effect of different crystalloid solutions on acid-base balance and early kidney function after kidney transplantation. Anesth Analg. 2008;107:264–9.
49. Butala NM, Reese PP, Doshi MD, Parikh CR. Is delayed graft function causally associated with long-term outcomes after kidney transplantation? Instrumental variable analysis. Transplantation. 2013;95(8):1008–14.
50. Premasathian N, Avihingsanon Y, Ingsathit A, Pongskul C, Jittiganont S, Sumethkul V. Risk factors and outcome of delayed graft function after cadaveric kidney transplantation: a report from the Thai Transplant Registry. Transplant Proc. 2010;42(10):4017–20.
51. Rehman S, Wen X, Casey MJ, Santos AH, Andreoni K. Effect of different tacrolimus levels on early outcomes after kidney transplantation. Ann Transplant. 2014;19:68–75.
52. Premasathian NC, Muehrer R, Brazy PC, Pirsch JD, Becker BN. Blood pressure control in kidney transplantation: therapeutic implications. J Hum Hypertens. 2004;18(12):871–7.
53. Juan Khong M, Ping Chong C. Prevention and management of new-onset diabetes mellitus in kidney transplantation. Neth J Med. 2014;72(3):127–34.
54. Wojtusciszyn A, Mourad G, Bringer J, Renard E. Continuous glucose monitoring after kidney transplantation in non-diabetic patients: early hyperglycaemia is frequent and may herald post-transplantation diabetes mellitus and graft failure. Diabetes Metab. 2013;39(5):404–10.

Kidney

21

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21.1 Donor Biopsy

The Expanded Criteria Donor (ECD) recommends histological evaluation of the kidney not only for donors over 60 but also for donors over 50 with comorbidities (firstly hypertension) even in the setting of normal serum creatinine [1]. The histological parameters to be evaluated include glomerular, vascular, tubular and interstitial injury. However, no studies have provided an absolute threshold beyond which a donor kidney must not be used, and there is no consensus on the value of biopsies for predicting graft function. Histological evaluation of the donor biopsy can be performed at harvesting by on call pathological examination or by means of implantation biopsies. Tissue sample analysis of implantation biopsies includes the immunohistochemistry (IHC) evaluation of C4d to identify pre-sensitized patients and immunofluorescence to highlight misdiagnosed glomerular diseases. The biopsies can be obtained through a wedge resection or needle core biopsy: superficial sampling in wedge resections can overestimate the glomerular sclerosis and fibrosis because the outer cortex is more sensitive to ischaemic damage (Fig. 21.1). Adequate sampling must contain at least 25 glomeruli and 2 arteries.

The pathological report of the donor biopsy includes:

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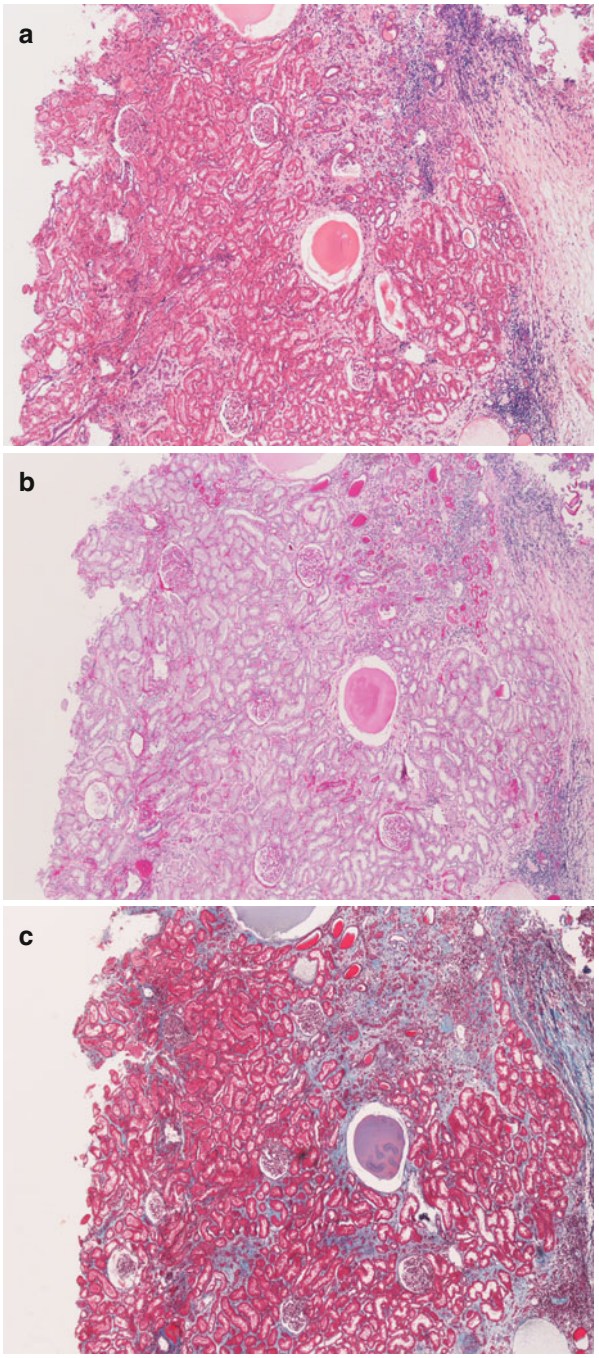


Fig. 21.1 A panoramic view of the donor biopsy stained with H&E (**a**), PAS (**b**) and trichrome stain (**c**) showing the ischaemic subcapsular area with inflammatory infiltrate, moderate fibrosis and obsolescent and sclerotic glomeruli. The punch biopsy can sometimes overestimate the real state of the kidney if the biopsy falls in such areas. Magnification 2×

- *Glomerular disease*
  - The percentage of sclerotic glomeruli. Glomerulosclerosis alone is not an independent predictor of graft function [2] even though glomerulosclerosis >10 % correlates with a major rate of delayed graft function (DGF), primary nonfunction and graft loss [3]. The degree of glomerulosclerosis can be a predictor of serum creatinine value at 12 months [4].
  - Any thrombotic microangiopathies (TMA) (Fig. 21.2). Glomerular fibrinoid thrombi can be dissolved by the graft recipient's fibrinolytic system without any anticoagulant therapy. In one series, some recipients experienced a primary nonfunction, while others had an initial DGF without any impairment of graft function at 2 years [2, 5, 6].
  - Any glomerular disease, i.e. lupus nephritis or diabetic glomerulonephropathies (Fig. 21.3). These features do not enter into the Karpinski score. Some studies suggest that diabetic kidneys can be used safely and that early diabetic lesions can regress with transplantation. However, no guidelines are currently available on the use of diabetic kidneys [7–9].
- *Vascular disease*
  - Fibro-intimal thickening of arteries and arteriolar hyalinosis. Moderate atherosclerosis (>25 % luminal narrowing) correlates to DGF, graft loss and higher creatinine serum levels [10–12].
  - Cholesterol emboli in the vascular tree may be correlated to DGF and impaired long-term renal function [13].
- *Tubulointerstitial disease*
  - The percentage of tubular atrophies and interstitial fibrosis (these parameters are usually comparable) yields a score based on the entity of damage [12, 14].
  - The presence and amount of acute tubular necrosis which can be associated with DGF.

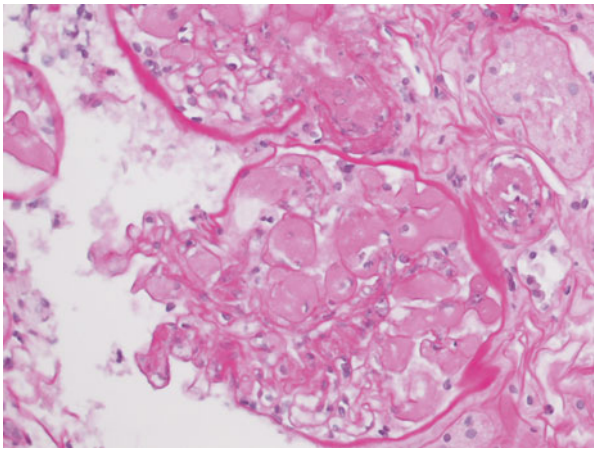


Fig. 21.2 At high magnification (PAS, 40×) the capillary lumen of the glomerulus is filled with a pale amorphous material extending into the vascular pole, occluding the lumen

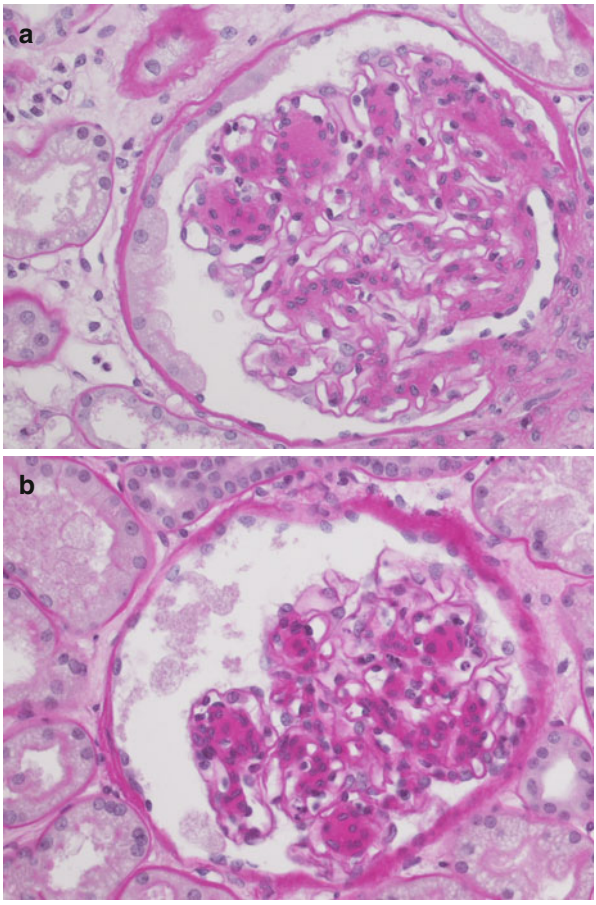


Fig. 21.3 The pictures (**a**, **b**) highlight the mesangial expansion with a nodular appearance. This feature does not enter into the Karpinski score. The biopsy in other fields showed just a mild interstitial and arterial intimal fibrosis without remarkable tubular atrophy. Magnification 40×, PAS

At our centre all these parameters are evaluated according to the Karpinski score system [12].

Glomerular score	
Score 0	No globally sclerotic glomeruli
Score1	<20 % globally sclerotic glomeruli
Score 2	20–50 % globally sclerotic glomeruli
Score 3	>50 % globally sclerotic glomeruli
Tubular score	
Score 0	Absent
Score 1	<20 % of tubules affected
Score 2	20–50 % of tubules affected
Score 3	>50 % of tubules affected
Interstitial score	
Score 0	No evidence of fibrosis
Score 1	<20 % of cortical parenchyma replaced by fibrotic tissue

Score 2	20–50 % of cortical parenchyma replaced by fibrotic tissue
Score 3	>50 % of cortical parenchyma replaced by fibrotic tissue
Vascular score (arterial fibrosis and arteriolar hyalinosis are evaluated, but the most severe lesion determines the final score)	
Score 0	Absent
Score 1	Increase in wall thickness that is less than the diameter of the lumen
Score 2	Increase in wall thickness that is equal to the diameter of the lumen
Score 3	Increase in wall thickness that exceeds the diameter of the lumen

21.1.1 Other Predictive Factors

- *Prediction of ischaemic injury effects*
  - Neutrophils in glomerular capillaries
  - Endothelial loss of capillaries (correlated to a transiently impaired function)
  - Tubular degeneration: necrosis or apoptosis of tubular cells, regenerative features with enlargement of tubular cell nuclei and simplification and loss of the brush borders of distal tubular cells
  - Tubular CAST (precipitation of proteinaceous amorphous/detritic material in renal tubules)
  - Microvascular thrombi in capillaries and small arteries without granulocytes
- *Prediction of acute rejection*
  - Neutrophils, macrophages and platelets in capillaries (glomerular and peritubular).
  - C4d deposition in peritubular capillaries may be predictive of acute antibody-mediated rejection (AMR).
- *Prediction of DGF*
  - Thrombotic angiopathy in glomerular capillaries

21.2 Surgical Complications

21.2.1 Ureteral Obstruction/Leak/Reflux

The presentation is with oliguria, haematuria and elevated creatinine. At histology only non-specific alterations can be seen: interstitial inflammation, oedema and tubular injury.

21.2.2 Lymphocele

Lymphocele consists in a collection of lymphatic fluid in the perinephric space. At histological examination the renal biopsy shows changes related to obstruction, with interstitial oedema, dilatation of the collecting ducts and mild inflammation.

21.2.3 Arterial/Venous Thrombosis

The clinical presentation is of macrohaematuria and acute renal failure. At histology, microthrombi and loss of the endothelium can be seen together with haemorrhage of the cortex and mild neutrophils in capillaries. The most important differential diagnosis is with acute cellular rejection (ACR) and hyperacute or AMR. Imaging findings (US and angiography) and immunohistochemistry for C4d lead to the correct diagnosis.

21.2.4 Arterial Stenosis

The clinical presentation is of DGF, hypertension and renal dysfunction. The histological picture may disclose cholesterol emboli (if the stenosis is due to an atheromatous plaque). Non-specific tubular atrophy with fibrosis or acute tubular injury (if the stenosis is intermittent) is evident.

21.3 Rejection

21.3.1 Hyperacute Rejection

Nowadays the incidence of *hyperacute rejection* is very low due to improved pretransplant testing for antibody against donor major antigens. The presentation is very rapid: from a few minutes (at the time of graft reperfusion) to a few days after transplantation, depending on the recipient's titres of specific antibody against the donor antigens. Anuria, primary graft nonfunction, fever, lack of perfusion by imaging studies, thrombocytopenia and increased circulating fibrin split characterize the clinical onset. At gross examination the graft is cyanotic, flaccid, haemorrhagic and oedematous with necrotic areas. Thrombosis of the renal artery can be found.

21.3.1.1 Histological Examination

Early features (1–12 h):

1. Platelet and neutrophil margination in glomerular and peritubular capillaries
2. Vascular congestion with scattered thrombi in glomerular capillaries and small arteries

Late features (12–24 h) include:

1. Interstitial oedema and haemorrhage
2. Widespread thrombotic microangiopathy
3. Fibrinoid arterial necrosis
4. Parenchymal necrosis

21.3.1.2 Ancillary Techniques

1. C4d peritubular capillaries and glomerular IHC staining.
2. Negative staining does not exclude a hyperacute rejection since C4d-negative cases are possible (related to decreased perfusion or to insufficient time to produce the C4d molecule, a product of the activation of the classical complement pathway).

21.3.1.3 Differential Diagnoses

1. Renal artery or vein thrombosis due to technical problems or hypercoagulable state (in these cases the thrombi are limited to the large vessels, and C4d staining is negative).
2. Perfusion nephropathy with loss of the endothelium. In this case congestion and thrombotic microangiopathy can be found without C4d staining.
3. Donor thrombotic microangiopathy.

21.3.2 Acute Humoral Rejection or Acute Antibody-Mediated Rejection

About 5–7 % of transplanted patients experienced an episode of antibody-mediated rejection (AMR) and a component of humoral rejection can be found in at least about 24 % of acute rejection cases. Presentation occurs from a few days to the first weeks after transplant, with anuria and acute renal failure. Circulating anti-donor-specific antibodies can be detected in about 90 % of recipients. At gross examination the graft is swollen, haemorrhagic and oedematous.

21.3.2.1 Histological Examination

- Glomeruli
  - Glomerulitis with neutrophils and mononucleated cells (complete or partial occlusion of at least one glomerular capillary with or without endothelial cell swelling, according to Banff 2013) [15, 16]
  - Occasional microthrombi in capillaries
- Tubules
  - Acute tubular injury represented by a simplification of tubular cells with loss of the brush border, ischaemic necrosis with loss of nuclei, thinning of the tubular cell cytoplasm and naked basal membranes
  - Tubulitis with neutrophil infiltrate
- Peritubular capillaries: dilatation and congestion of capillaries filled with neutrophils and occasional microthrombi
- Interstitium: oedema, occasionally haemorrhagic areas, inflammatory infiltrate predominantly with neutrophils

- Vessels
  - Necrosis of the media with fragmentation of the *lamina elastica* and fibrinoid necrosis
  - Inflammatory cells within the vessel wall
  - Activation of capillary and artery endothelial cells showing plump cytoplasm and nuclear enlargement

21.3.2.2 Ancillary Techniques

- IHC positivity for C4d along the peritubular and glomerular capillaries (Fig. 21.4). Early biopsies may not disclose C4d deposition, but this does not rule out a diagnosis of AMR since this may become positive in repeated biopsies taken after 1–3 days. Conversely, some studies have demonstrated that positive immunostaining for C4d in protocol biopsies appears before the clinical manifestation of an AMR episode [17].

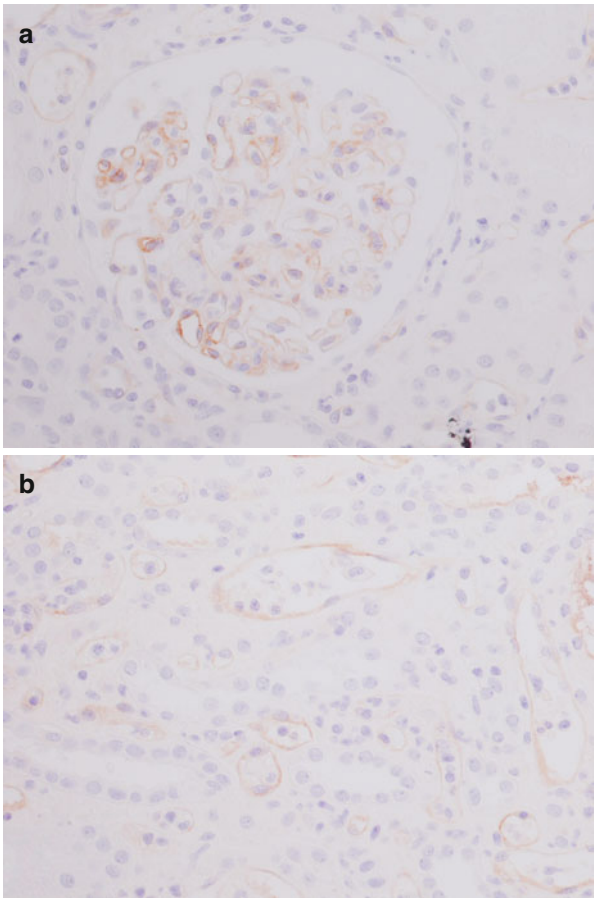


Fig. 21.4 Immunohistochemical stain for C4d shows a diffuse and continuous linear positivity in glomerular (**a**) and along peritubular capillaries (**b**). Magnification 20×

- IHC staining for CD68 does not improve the sensitivity of identifying glomerulitis when the Banff 2013 definition is applied.
- Wide and diffuse immunopositivity for C4d at immunofluorescence (IF), which is more sensitive than IHC.

21.3.2.3 Diagnostic Criteria (Banff Classification)

The definition of AMR has now been revised [15]: histological evidence of acute tissue injury (glomerulitis and/or peritubular capillary infiltration and/or acute thrombotic microangiopathy and/or tubular necrosis) (Fig. 21.5) must be present together with evidence of a recent endothelial/antibody reaction (positivity for C4d IHC and/or microvascular inflammation highlighted by glomerulitis or peritubular capillaritis) and serological evidence of anti-donor-specific antibodies.

The histological pattern can be graded from grade 1 with acute tubular damage and minimal inflammatory infiltrate to grade 2 with peritubular capillaritis or glomerulitis with occasional microthrombi or grade 3 with fibrinoid arterial necrosis. The presence of only one or two of these criteria leads the pathologist to a diagnosis of "suspect" AMR (Fig. 21.6).

Biopsies with a C4d-positive immunostaining without any inflammation can be considered a kind of "accommodation".

21.3.2.4 Differential Diagnoses

- Acute cellular rejection: generally the infiltrate is composed predominantly of T lymphocytes. Fibrinoid necrosis of renal small arteries, glomerulitis, microvascular thrombosis and areas of infarction are less prominent [18].
- Chronic humoral rejection: the clinical setting shows a slow decline.
- Accommodation: C4d deposition in the absence of an inflammatory reaction.
- Acute tubular injury/acute tubular necrosis: simplification of the renal tubules with loss of nuclei, thinning of tubular cell cytoplasm and naked basal membranes in the absence of an inflammatory reaction. C4d is negative.
- Acute pyelonephritis: dirty casts in the tubules (composed of neutrophils and necrotic material) with a diffuse infiltrate of neutrophils in the parenchyma. A positive urine culture and C4d negativity favour the diagnosis.
- Thrombotic microangiopathies: due to drug toxicity or recurrent disease. There is no C4d immunoreactivity.

21.3.3 Acute Cellular Rejection or T-Cell-Mediated Rejection

Acute cellular rejection (ACR) involves 5–10 % of kidney recipients in the first year posttransplant, generally in the first few weeks. The frequency tends to decline after the first 6 months, but ACR can arise at any time in the recipient. In acute renal failure increased serum creatinine concentration, decline in urine output and oliguria, weight gain, fever and malaise define the clinical picture. Circulating anti-donor-specific

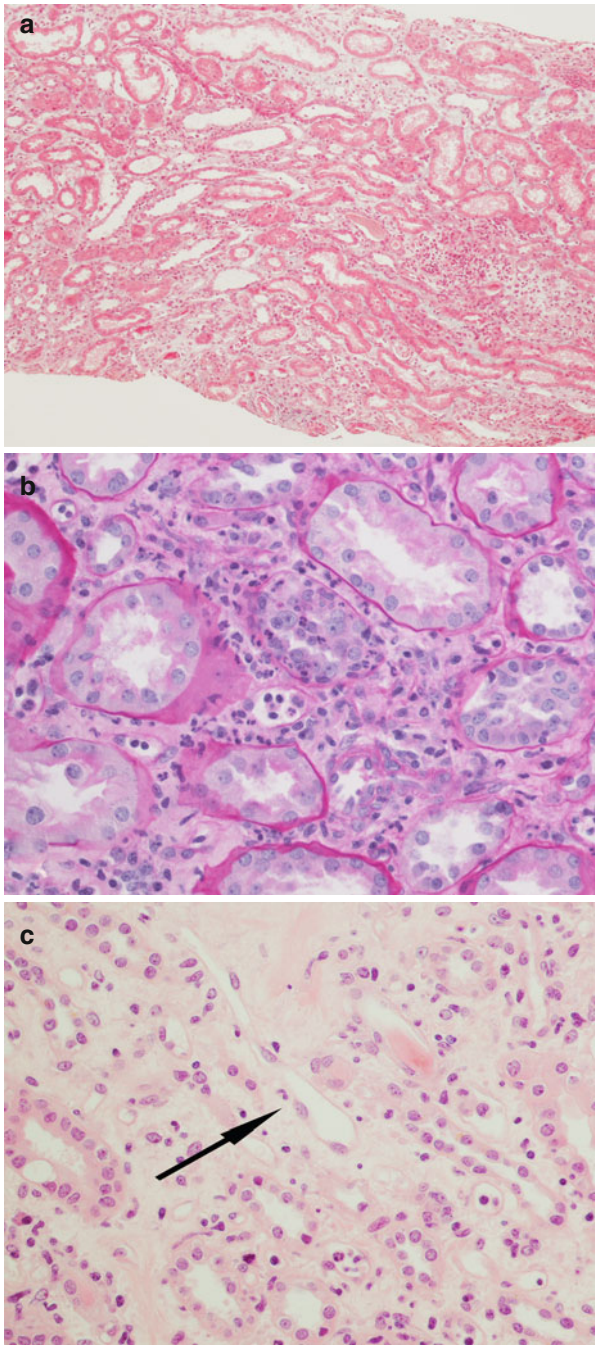
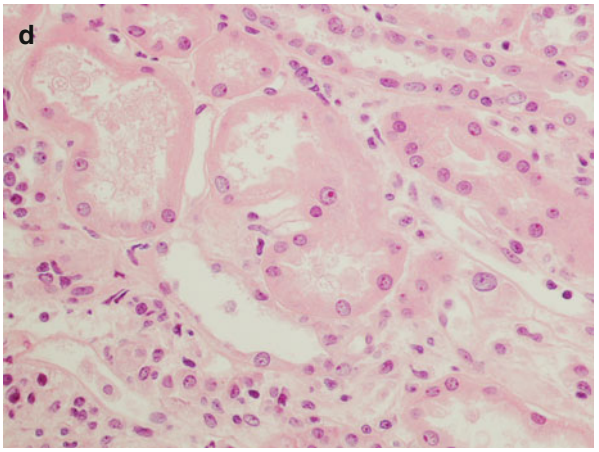
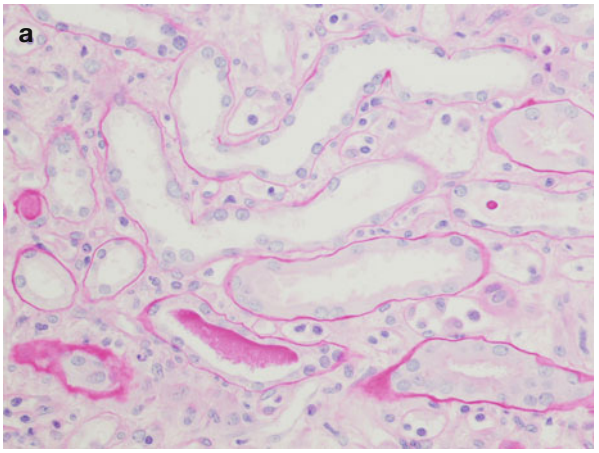


Fig. 21.5 In AMR there is a diffuse interstitial oedema highlighted by the *pale light green* trichrome stain (**a** magnification 4×), tubulitis with neutrophil infiltrate (**b** PAS, magnification 20×), activation of the endothelial cells (*arrow*, **c** H&E, magnification 40×) and acute tubular necrosis (**d** H&E, magnification 40×)

Fig. 21.5 (continued)





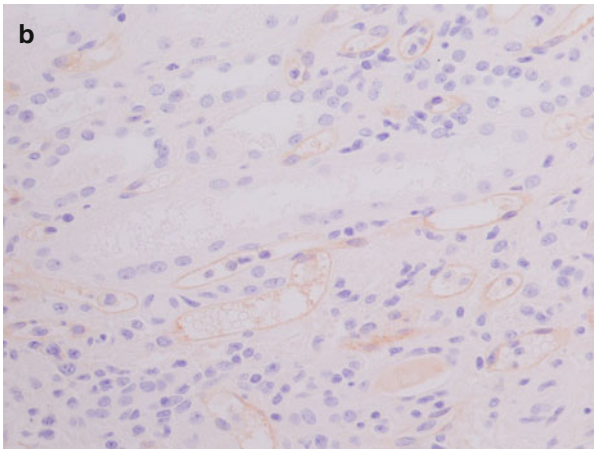


Fig. 21.6 This is a biopsy 5 days after kidney transplantation in a patient with oliguria. The histological pictures (**a** PAS, magnification 40×) demonstrated only an acute tubular necrosis of the parenchyma with a mild peritubular capillaritis without any interstitial inflammatory infiltrate or tubulitis. The main differential diagnosis is with a tubular cell necrosis with a delayed graft function. The C4d stain (**b** magnification 40×) reveals a diffuse deposition of the molecule along the peritubular capillaries: the patient was given a steroid bolus before the biopsy because of the clinical suspicion of AMR

antibodies can be detected in about 90 % of recipients. At US the graft becomes enlarged, oedematous and tender. At gross examination the graft is swollen, pale, haemorrhagic with congestion of the medulla, and oedematous. Foci of infarction may be evident on the cortex.

21.3.3.1 Histological Examination

- Glomeruli
  - Only occasional mild inflammatory infiltrate of mononuclear cells (generally in only 10 % of cases) in glomeruli with mild reactive swelling in endothelial cells (Fig. 21.7a).
  - In <5 % of cases a severe mononuclear cell glomerular infiltrate (*acute allograft glomerulopathy*) can be found, giving the appearance of endocapillary hypercellularity. Endothelial injury with areas of mesangiolysis is associated. This picture is often seen in the setting of moderate ACR with endoarteritis, but it can also represent the only histological feature of rejection.

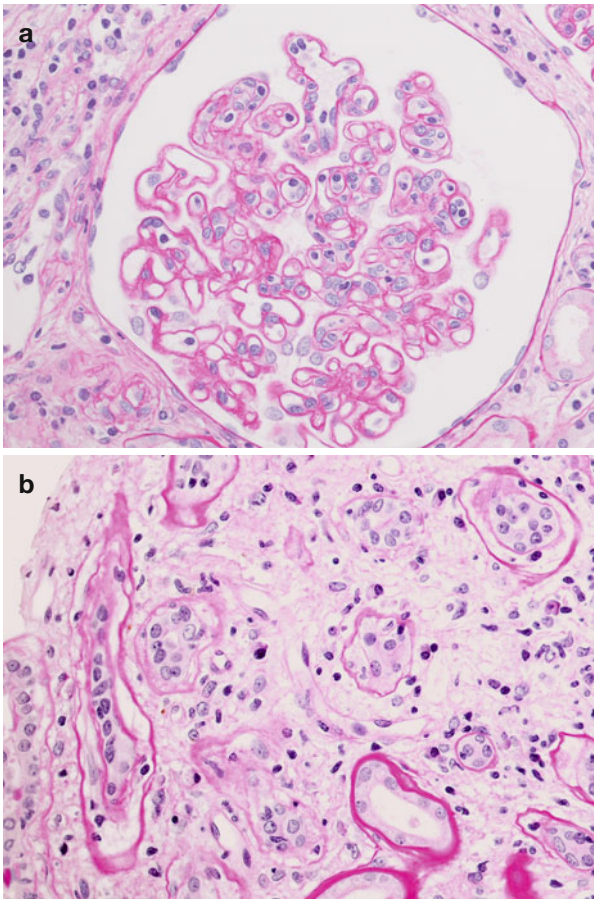


Fig. 21.7 The picture on the *left* (**a** PAS, magnification 40×) shows a mild inflammatory infiltrate of mononuclear cells in the glomerulus, while the picture on the *right* (**b** PAS, magnification 40×) shows marked tubulitis: note the lymphocytes between the tubular epithelium and the basement membrane and the moderate interstitial oedema

- Tubules
  - Tubulitis with T-cell lymphocytes (CD8+) (Fig. 21.7b)
  - Tubular cell injury, occasionally with a granulomatous reaction
- Interstitium
  - Oedema, occasionally with haemorrhagic areas.
  - Chronic inflammatory infiltrate (involving at least 25 % of the cortex) with a predominance of T-cell lymphocytes and macrophages (Fig. 21.8). Macrophages/monocytes can be the major cell type, notably in the setting of T-cell-depleting drugs (such as CAMPATH 1).
  - A plasma cell-rich subset and a CD20+ B-cell-rich subset AR have a worse prognosis.
- Peritubular capillaries: dilatation and mononuclear cell infiltrate

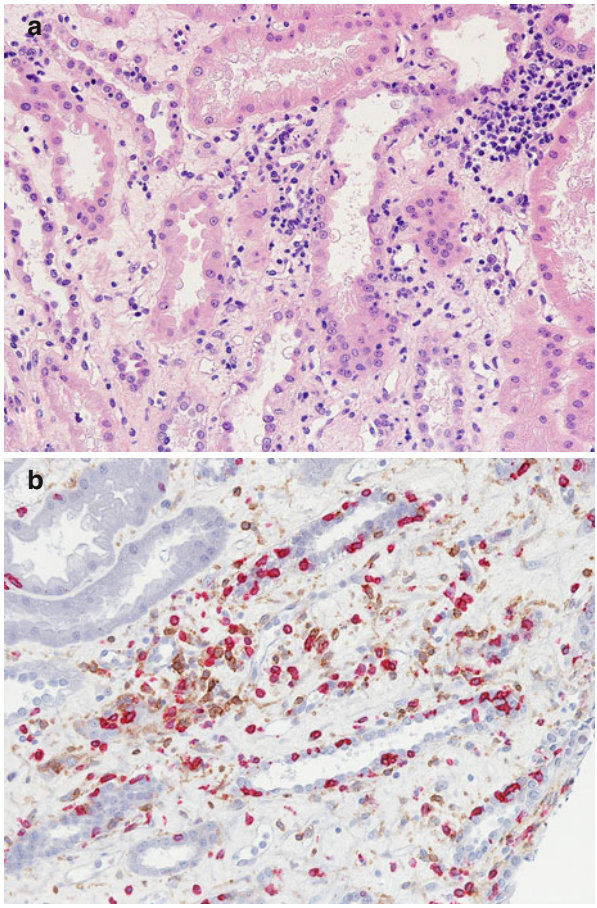


Fig. 21.8 The picture on the *left* (**a** PAS, magnification 20×) shows a chronic inflammatory infiltrate: the double immunostaining for T lymphocytes CD4/CD8 (**b** magnification 20×) shows that the tubulitis is caused by CD8+ T-cell lymphocytes (in *red*) and that the CD4+ T-cell lymphocytes (in *brown*) are localized predominantly in perivascular and interstitial sites

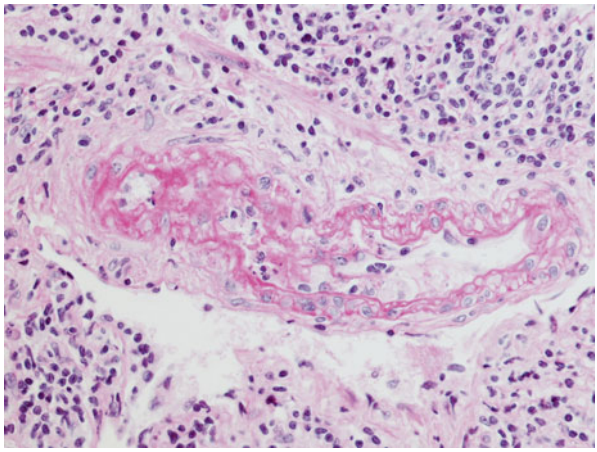


Fig. 21.9 A case of ACR type 3 with transmural arterial inflammation and fibrinoid necrosis (PAS, magnification 40×)

- Vessels
  - T cells within the lumen of small arteries (endarteritis) with endothelial injury.
  - Activation of endothelial cells of capillaries and arteries.
  - In severe cases the inflammatory infiltrate is transmural with myocyte necrosis (Fig. 21.9).

21.3.3.2 Ancillary Techniques

- Immunostaining for C4d is negative. C4d positivity can highlight a concomitant AHR component.

21.3.3.3 Grading According to Banff Classification [16]

1. ACR type 1 or tubulointerstitial. inflammatory infiltrate in at least 25 % of the cortex together with foci of moderate tubulitis (1A) or severe tubulitis (1B).
2. ACR type 2 with endarteritis. It is then subdivided into 2A when the infiltrate affects <25 % of the luminal areas and 2B when the infiltrate affects ≥25 % of the luminal areas.
3. ACR type 3 with transmural arterial inflammation associated with myocyte foci and fibrinoid necrosis.
4. Suspicious/borderline for ACR. Inflammatory infiltrate in <20 % of the cortex associated with mild tubulitis.

21.3.3.4 Differential Diagnoses

- Polyomavirus infection (BK): typically BK shows a more evident plasma cell infiltrate with tubular cell intranuclear viral inclusions, also detectable in the urine and with IHC on biopsy.
- Cytomegalovirus infection: tubular cell intranuclear viral inclusions detectable with IHC on biopsy.

- Pyelonephritis: a neutrophil infiltrate with dirty tubular casts; the infection can be confirmed by a positive urine culture.
- Posttransplant lymphoproliferative disease (PTLD): monotonous infiltrate of B lymphocytes. Tubulitis and endarteritis can be present. The in situ *hybridization* for EBV-RNA is diagnostic.
- Drug-induced tubulointerstitial nephritis: an eosinophilic-rich infiltrate is evident, sometimes infiltrating tubular cells.
- Thrombotic microangiopathy (TMA): endoluminal thrombi in small arteries in the absence of endarteritis. Mucoid intimal thickening with progressive luminal obstruction appears.

21.3.4 Chronic Rejection

Ten years after transplantation, about 20 % of patients lose their grafts due to CR, defined as a progressive loss of the graft due to a continuous humoral or cellular immunological reaction against the donor antigens. Clinical presentation is characterized by progressive renal failure, proteinuria and hypertension.

Depending on the kind of immunological mechanism involved, CR can be distinguished in:

- Chronic humoral rejection (CHR) or chronic antibody-mediated rejection
- Chronic cellular rejection (CCR)

21.3.5 Chronic Humoral Rejection

The diagnosis of CHR has been revised as a category of AMR (see above) according to Banff 2013. This diagnosis requires the histological picture, evidence of an endothelial/antibody reaction (defined by the C4d IHC positivity and/or microvascular inflammation) and serological evidence of anti-donor-specific antibodies.

21.3.5.1 Histological Examination

- Glomeruli
  - Transplant glomerulopathy (or chronic glomerulopathy, CG) (Fig. 21.10a) defined as duplication of the glomerular basement membrane (BM) (railway track) identified in at least one glomerular capillary loop (revised according to Banff 2013) [15]. The definition of CG 1a was introduced when the double contour is detectable only at electron microscopy and CG1b when the double contour is also evident at histology.
  - Glomerulitis with prevalent monocyte/mononuclear cells (CD68+) (Fig. 21.10b).
  - Possible mesangial expansion and sclerosis.

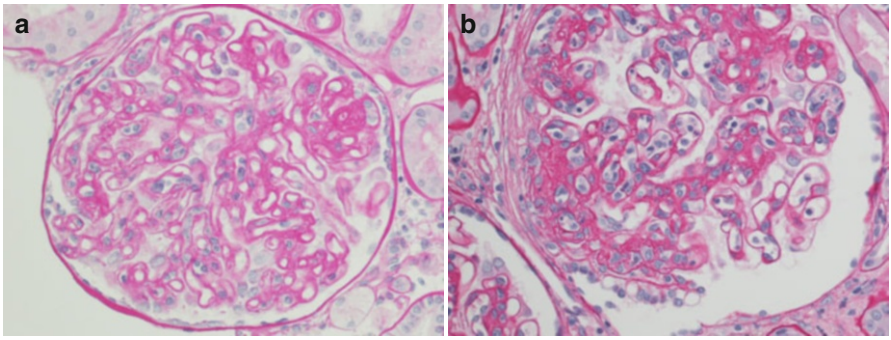


Fig. 21.10 On the *left* (**a**) a moderate/severe case of transplant glomerulopathy with duplication of the basement membrane of the glomerular capillary tuft (PAS, magnification 40×). On the *right* (**b**) a case of glomerulitis associated with moderate mesangial expansion together with a thickening of the glomerular basement membrane (PAS, magnification 40×)

- Tubules
  - Atrophic tubules with occasional thickening of the basement membrane with duplication (Fig. 21.11)
- Interstitium
  - Fibrosis
  - Mild chronic inflammatory infiltrate
- Peritubular capillaries
  - Dilatation and mononuclear cell infiltrate (peritubular capillaries)
  - Duplication of the BM, generally best seen by electron microscopy
- Arteries
  - Fibrous intimal thickening with luminal narrowing, incorporating T lymphocytes and macrophages (transplant arteriopathy or chronic allograft arteriopathy). The intima shows concentric thickening without multilayering of the lamina elastica (characterizing vascular hypertensive damage): at the beginning a loose matrix is evident, becoming more fibrotic as it evolves into an "onionskin" appearance (Fig. 21.12). The media generally shows no marked alteration.

21.3.5.2 Ancillary Techniques

- Evidence of C4d deposition along peritubular and glomerular capillaries

21.3.5.3 Differential Diagnoses (Transplant Glomerulopathy)

- Chronic thrombotic microangiopathy associated with calcineurin inhibitor toxicity or a history of haemolytic uraemic syndrome. The absence of intracapillary fibrin thrombosis with necrosis, the anamnesis and other signs of immunosuppressive drug toxicity may help in the diagnosis.

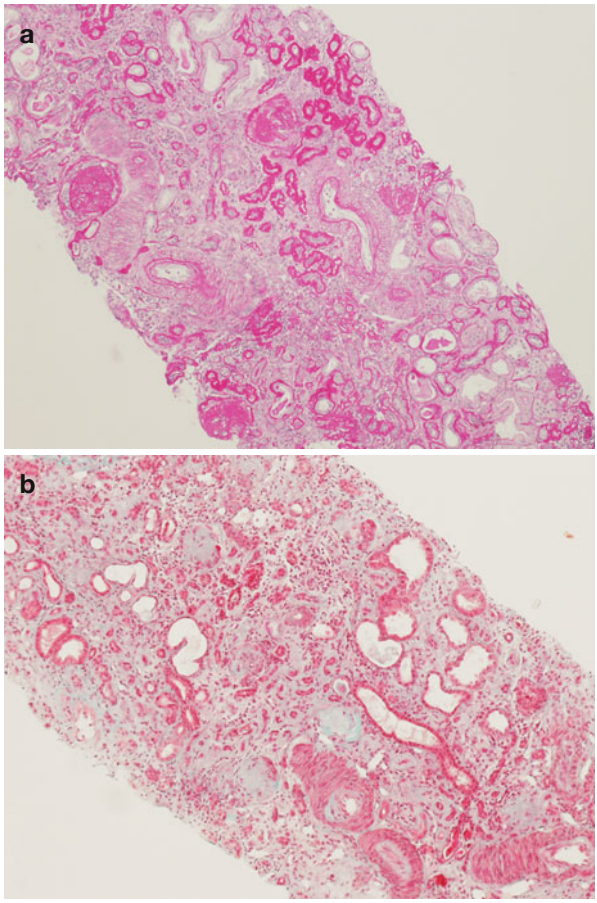


Fig. 21.11 The picture (**a** PAS, magnification 4×; **b** trichrome stain, magnification 4×) demonstrates a mild chronic inflammatory infiltrate with diffuse tubular atrophy and totally sclerotic glomeruli. There is also severe chronic vascular damage

- Immune complex glomerulonephritis recurrent or de novo. This diagnosis requires a positive IF pattern and the typical immunocomplex at electron microscopy. The anamnesis is helpful.

21.3.5.4 Differential Diagnoses (Transplant Arteriopathy)

- Arteriosclerosis. Elastic fibre accumulation and thickening of the media in the absence of an inflammatory infiltrate in the vessel wall are more typical of a hypertensive injury. Evaluation of the donor biopsy can help distinguish lesions already present in the kidney prior to transplantation. Notably arteriosclerosis may coexist with transplant arteriopathy.
- Chronic thrombotic microangiopathy. The disease typically affects the smaller arteries, in contrast to rejection that is more evident in medium-sized vessels.

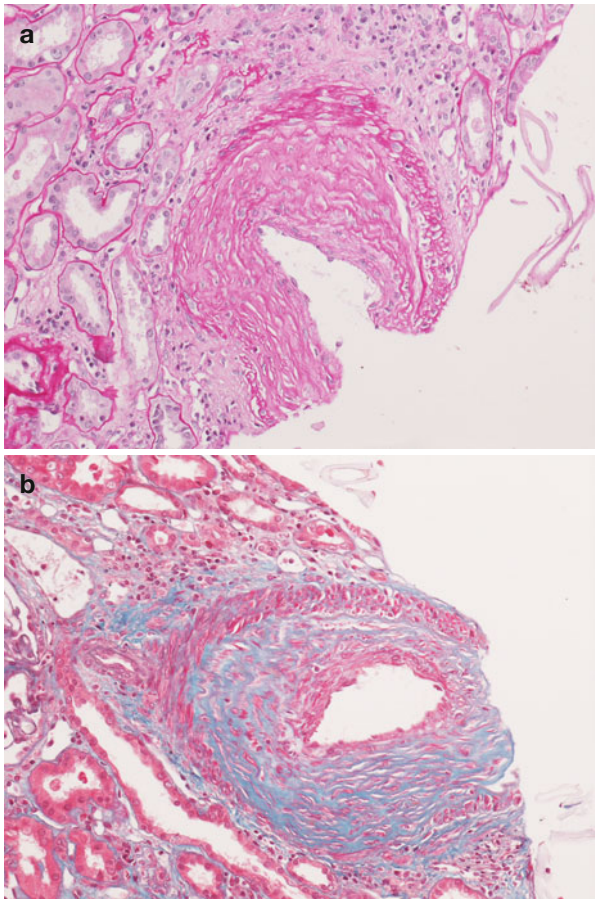


Fig. 21.12 The intima shows concentric thickening creating an "onionskin" appearance without any particular alteration of the media. (**a**) PAS, 20×; (**b**) trichrome stain, 20×

21.3.5.5 Differential Diagnoses (Tubulointerstitial Lesions)

- Calcineurin inhibitor toxicity associated with other signs of immunosuppressive drug toxicity such as nodular arteriolar hyalinosis.
- Chronic obstruction leads to an interstitial fibrosis with tubular atrophy in the absence of a diffuse inflammatory mononuclear infiltrate.

21.3.6 Chronic Cellular Rejection

21.3.6.1 Histological Examination

- Glomeruli
  - Global glomerulosclerosis
  - Focal/segmental sclerosis with adhesions

- Tubules
  - Tubulitis and atrophic tubules
- Interstitium
  - Fibrosis
  - Mononuclear inflammatory infiltrate meeting the criteria of ACR
- Arteries
  - The same alterations as for CHR

21.3.6.2 Ancillary Techniques

- There is no evidence of C4d deposition along peritubular and glomerular capillaries.

21.3.6.3 Differential Diagnoses

- CHR. This situation presents transplant glomerulopathy and multi-lamination of the basement membrane of peritubular capillaries and tubules together with C4d positivity.
- Calcineurin inhibitor toxicity. See below.
- Hypertensive arteriosclerosis. See below.

21.4 Calcineurin Inhibitor Toxicity

21.4.1 Histological Examination

- Tubule*s*. The most common tubular alteration is the so-called isometric vacuolization of the cytoplasm, found more frequently in the proximal tubules and sometimes associated with a loss of tubular cell brush borders (Fig. 21.13a, b). The lesion is reversible with dose reduction. Other alterations include giant mitochondria and dystrophic microcalcification.
- Arterioles and arteries. Commonly the alterations are present in the arterioles; when very diffuse they can also be found at the vascular pole of the glomeruli. The early lesion is a marked swelling of the muscular cells of the media with clearing of the cytoplasm that evolves into a diffuse hyalinosis (nodular accumulation of hyaline material along the media replacing the necrotic smooth muscle cells of the media) (Fig. 21.13c, d). This lesion can be found within a few days after transplant, and a cumulative use of the drug can induce arteriolopathies in close to 100 % of allografts after 10 years [19]. In the most severe cases, calcineurin toxicity can induce a TMA with fibrin thrombi in capillaries and mucoid intimal thickening with oedematous swelling of the arterioles that evolves into a sclera-fibrotic lesion with an “onionskin” appearance.

  The Banff 1997 scheme, adapted by Mihatsch, is used to score calcineurin inhibitor hyaline arteriolopathies [20].

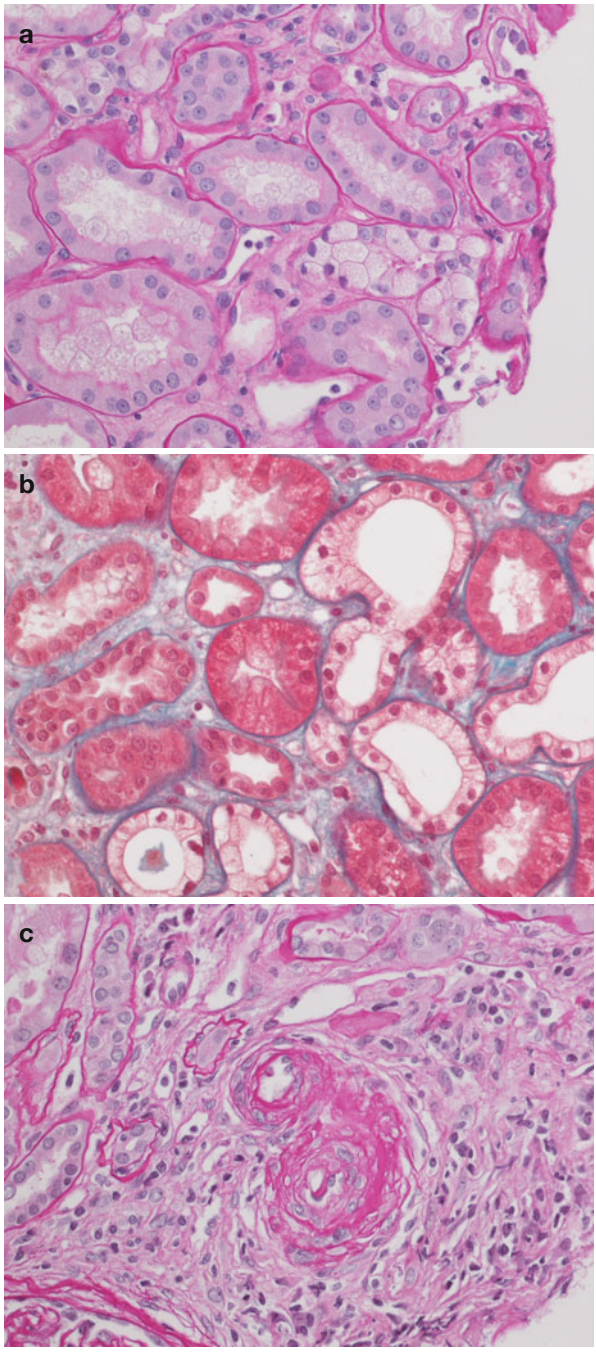
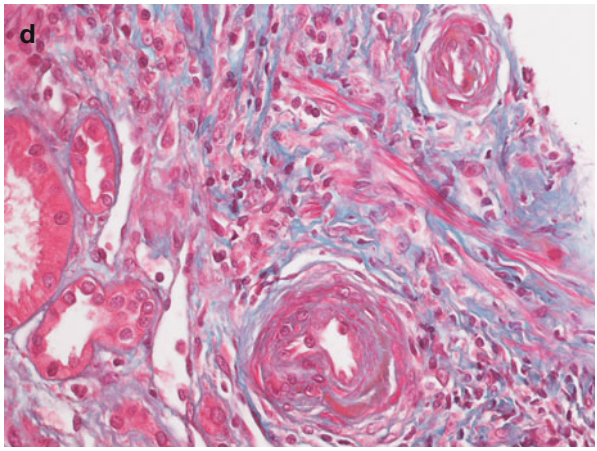


Fig. 21.13 The picture presents the classical tubular "isometric vacuolization" of the cytoplasm (**a** PAS, magnification 40×; **b** trichrome stain, magnification 40×) and arteriolar hyalinosis (**c** PAS, magnification 40×; **d** trichrome stain, magnification 40×)

Fig. 21.13 (continued)



- Glomeruli. The glomeruli can be affected as a direct effect of the calcineurin inhibitor or as a consequence of vascular damage: the end point, however, is sclerosis. Sometimes glomerular basement membrane duplication can be found but only focally and segmentally, together with mesangial expansion (the so-called calcineurin inhibitor glomerulopathy that enters the differential diagnosis with the "transplant glomerulopathy").

  Focal segmental glomerulosclerosis, the collapsing variant, is another glomerular lesion that can be an expression of drug damage.
- Interstitium. Typically there is a sparse and mild inflammatory infiltrate, with a "striped" fibrosis. In acute toxicity mild oedema can occasionally be found.

21.4.1.1 Differential Diagnoses

- Tubules. Tubular cell vacuolization can also be found in osmotic nephrosis following therapy with plasma cell expanders, radiolabelled contrast media or intravenous immunoglobulin solution. Giant mitochondria are also found in cases of ischaemic damage, and dystrophic calcification can be the consequence of marked acute tubular necrosis (as ischaemic/reperfusion damage).
- Arterioles and arteries. Hypertension and metabolic changes such as diabetes mellitus can induce arteriolar hyalinosis. In hypertension damage the hyaline deposits are subendothelial (and not in the media of the vascular wall) with an intact or atrophic appearance of the muscle cells of the media. Diabetes mellitus injury, however, is histologically similar to that of calcineurin inhibitors.

- Glomeruli. A partially duplicated basement membrane in the glomeruli involves three major differential diagnoses:
  1. A late phase of a TMA not induced by a calcineurin inhibitor (e.g. a recurrence of the recipient disease or a de novo TMA caused by other drugs): this condition has to be considered in the correct clinical setting.
  2. Membranoproliferative glomerulonephritis (de novo or recurrent): this situation has to be confirmed by typical IF and electron microscopic examination.
  3. Transplant glomerulopathy in the setting of chronic rejection.

21.5 Posttransplant Lymphoproliferative Disorder

21.5.1 Epidemiology

PTLD is one of the most common posttransplant malignancies (>90 %), representing the most common posttransplant cancer in children and the second most common malignancy after skin cancer in adults. The incidence of PTLD in renal transplant recipients is 1 %, and the renal allograft is affected in >30 % of cases [21, 22].

21.5.1.1 Clinical Features

- Fever.
- Lymphadenopathy.
- Extranodal involvement occurs in more than two thirds of cases and may also involve the allograft. The central nervous system is frequently involved (in up to 30 % of cases) and can be the only site of disease.

21.5.1.2 Macroscopic Examination

In section, the kidney surface presents a bloated and blurred corticomedullary junction, diffuse petechiae and vaguely nodular involvement.

21.5.1.3 Histological Examination

The 2008 World Health Organization (WHO) [23] classification system recognizes four major histopathological subtypes of PTLD:

1. Early hyperplastic lesions
2. Polymorphic lesions (polyclonal or monoclonal)
3. Monomorphic lesions (B, T, NK)
4. Classic Hodgkin-type lymphomas:

Plasmacytic Hyperplasia (PH) and Infectious Mononucleosis-like PTLD

This entity usually occurs in young patients and appears as a mononucleosis-type acute infectious illness characterized by polyclonal B-cell proliferation with no

evidence of malignant transformation: the lymphoid follicles are floridly reactive or hyperplastic. In these cases EBV infection can often be demonstrated.

Polymorphic PTLD
This entity can have polyclonal or monoclonal lymphoid infiltrates with evidence of malignant transformation but does not fulfil all the criteria for typical B-cell or T-/NK-cell lymphomas. At histology, there is an effacement of the underlying tissue with a mixed infiltrate: immunoblasts, plasma cells and small–intermediate-sized lymphoid cells. Areas of geographic necrosis may be present with a high mitotic rate and nuclear atypia; EBV infection can often be demonstrated.

Monomorphic PTLD
This is a monoclonal lymphoid proliferation meeting the criteria for one of the B-cell or T-/NK-cell lymphomas recognized in immunocompetent patients. Burkitt lymphoma (BL) or plasma cell neoplasms occur less frequently. The WHO 2008 does not include small B-cell lymphoid neoplasms (e.g. follicular lymphomas, small lymphocytic lymphoma) and marginal zone (MALT) lymphomas arising in the posttransplant setting among the PTLD. At histological examination destruction of the underlying parenchyma is evident, and the lymphoid infiltrate shows malignant cytological features.

Classic Hodgkin-Type Lymphomas
This rare form of PTLD shows the histology of classic Hodgkin lymphoma and can be seen as a late complication of transplantation. Biopsy shows Reed-Sternberg cells and variants on a mixed background of small lymphocytes, histiocytes and eosinophils.

21.5.1.4 Differential Diagnoses

- Rejection. Tubulitis and endarteritis may be present. Rejection shows a predominance of T lymphocytes and macrophages; negativity for EBER-1 in situ hybridization for EBV provides further assurance that the cases classified as acute rejection did not have complicating PTLD lesions.
  - Inflammatory or infectious conditions.
  - EBV-positive spindle-cell neoplasms.

21.6 Infection

Over 50 % of transplant patients have at least one infection in the first year following transplantation [24], and the risk of contracting any specific infection changes according to the posttransplant period. Within the first month the weakening effects of immunosuppression have not been completely realized, and more than 90 % of infections are caused by bacterial or fungal agents. Conversely, from 1 to 6 months after transplantation, viruses are the most frequent cause of infections [25].

21.6.1 CMV Infection

Cytomegalovirus (CMV) remains one of the most important pathogens and results in a significant morbidity and mortality in kidney transplant recipients. About 20–60 % of patients develop symptomatic CMV infection [26], which may increase the incidence of infections, acute rejection, chronic allograft nephropathy and chronic vascular injury with adverse effects on the long-term outcome of both the patient and allograft [27].

21.6.1.1 Histological Examination

1. Large intranuclear inclusions in tubular epithelial cells (rare in endothelial cells) with variable degrees of interstitial inflammation
2. Large eosinophilic intranuclear inclusions in endothelial cells; thrombotic microangiopathy
3. Acute glomerulonephritis (rare): endocapillary hypercellularity, crescents and inclusions in glomerular endothelial cells

21.6.1.2 Differential Diagnoses

- Polyomavirus nephropathy: see below.
- Adenovirus tubulointerstitial nephritis: tubular necrosis, granulomatous inflammation.
- ACR: tubulitis, interstitial inflammation and endarteritis.
- Acute allograft glomerulopathy: mesangiolysis, C4d-negative immunohistochemistry and no virus inclusion.
- Acute glomerulonephritis: glomerular immune complexes evident with IF.

21.6.2 Polyomavirus (BKV) Infection

BKV is a ubiquitous double-stranded DNA virus representing a major pathogen in kidney transplantation. The clinical presentation is variable: from completely asymptomatic to allograft dysfunction and graft loss. BKV nephropathy may precede or follow a treatment for acute rejection [28]. Screening for decoy cells in the urine is a useful tool, but diagnosis of BKV nephropathy requires identification of the virus in kidney tissue by either IHC or electron microscopy. PCR quantification of viraemia appears to correlate with the likelihood of BKV nephropathy and serves as a guide in monitoring response to therapy.

21.6.2.1 Histological Examination

- Interstitial mononuclear inflammation (Fig. 21.14)
- Nuclear inclusions in tubular epithelium (confirmed by IHC) (Figs. 21.15 and 21.16)
- Tubulitis
- Immune complex deposition

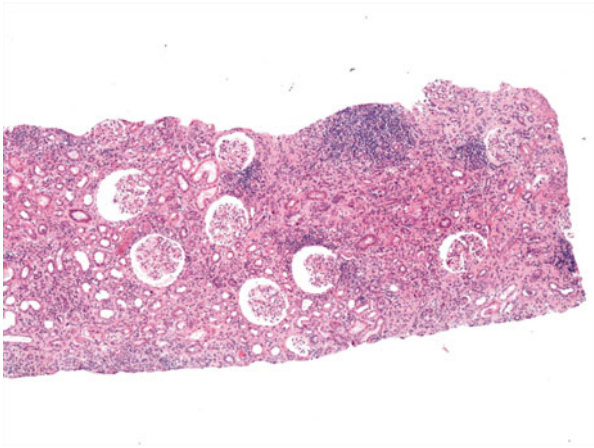


Fig. 21.14 H&E (magnification 4×) shows a diffuse inflammatory interstitial infiltrate

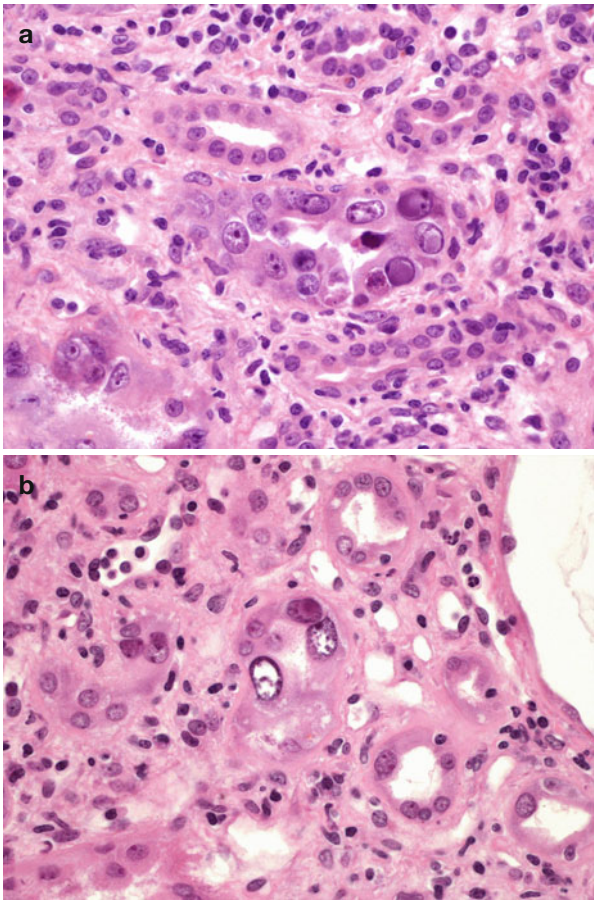


Fig. 21.15 Light microscopy at high power (H&E, magnification 40×) shows the typical cytopathic viral changes of the tubular cells. The images (**a**, **b**) show two of the four typical nuclear alterations: ground-glass intranuclear inclusions and the nuclear vesicular changes with irregular chromatin and occasional nucleoli

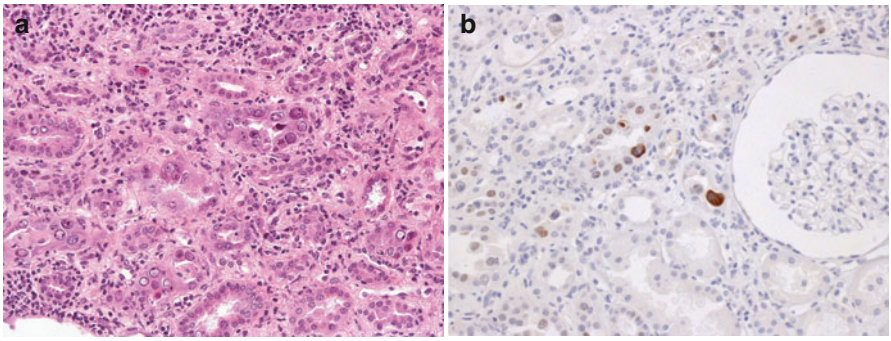


Fig. 21.16 H&E on the *left* (**a**, magnification 20×) shows the typical tubular nuclear alteration of the infection: a positive SV40 immunohistochemistry (**b**, on the *right*, magnification 20×) confirms the diagnosis

21.6.2.2 Differential Diagnoses

- Acute tubular interstitial rejection (type 1): tubulitis with interstitial inflammation
- Adenovirus tubular necrosis: prominent interstitial inflammation
- Acute tubular necrosis: reactive atypia of tubular epithelial cells
- Acute interstitial nephritis: marked interstitial inflammation, no intranuclear inclusion

21.6.3 Adenovirus Infections

Adenoviruses (AdV) are emerging pathogens in solid organ transplant recipients with clinical manifestations ranging from subclinical infection to fatal outcome. The reported prevalence of AdV infection during the first year after kidney transplant is about 11 % by urine culture and 6.5 % by serum PCR [29]. Renal allograft involvement is rare, and the infection has a broad range of histological manifestations: tubular cell necrosis with cytopathic viral effects together with interstitial inflammation without glomerular or vascular involvement or as necrotizing tubulointerstitial nephritis and space-occupying lesions with or without ureteral obstruction [30]. The common differential diagnoses include BK- and CMV-mediated interstitial nephritis.

21.6.3.1 Histological Examination

Severe necrotizing granulomatous lesions with predominant neutrophilic inflammation can be considered characteristic for AdV infection. Additional features that are more pronounced in AdV interstitial nephritis include mixed cellular infiltration with macrophages and histiocytes and tubular basement membrane disruption.

21.6.3.2 Differential Diagnoses

The presence of granulomatous interstitial nephritis enters the differential diagnosis with mycobacterial, fungal (histoplasmosis, *Cryptococcus* species and *Candida albicans)* and viral (adenovirus, HIV, CMV and BKV) infections. Granulomas around tubules represent a useful feature pointing to adenovirus. The virus can be confirmed using in situ hybridization studies. Other differential diagnoses are drug-induced nephritis, antineutrophil cytoplasmic autoantibody-associated vasculitis and sarcoidosis. Rarely, AdV and cellular rejection may coexist and pose a diagnostic challenge. In such conditions, overriding tubulitis, vasculitis and predominant T-lymphocyte infiltration should favour the diagnosis of rejection.

21.7 Drug-Induced Acute Interstitial Nephritis

Myriad drugs have been implicated in causing acute interstitial nephritis (AIN). Drugs are more often recognized as aetiologic factors in AIN because of the increased frequency in using drugs, the increased use of renal biopsy and the typical clinical presentation [31]. Some classes of medication are often associated with certain clinical features of AIN. The development of drug-induced AIN is not dose related and may become clinically evident from 2 weeks or longer after starting medical therapy.

21.7.1 Histological Examination

The hallmark of AIN is an interstitial inflammatory infiltrate with oedema, sparing the glomeruli and blood vessels. Interstitial fibrosis is mild and develops later in the disease. The inflammatory infiltrate is composed of mononuclear cells and T lymphocytes, with a variable number of plasma cells and eosinophils. Eosinophils may be totally absent from the infiltrate or may concentrate in small foci, forming eosinophilic microabscesses. In chronic interstitial nephritis, the cellular infiltrate is largely replaced by interstitial fibrosis.

21.8 De Novo or Recurrent Glomerular Disease

A glomerular disease is deemed de novo when the allograft develops a disease different from that of the native kidney. It is important to know exactly the cause that led to end-stage renal failure to exclude a recurrent disease. De novo or recurrent glomerular disease has the same histological features and IF pattern as those of the native kidney.

References

1. Haas M. Donor kidney biopsies: pathology matters, and so does the pathologist. Kidney Int. 2014;85:1016–9.
2. Pokorná E, Vítko S, Chadimová M, Schück O, Ekberg H. Proportion of glomerulosclerosis in procurement wedge renal biopsy cannot alone discriminate for acceptance of marginal donors. Transplantation. 2000;69:36–43.
3. Mizuiri S, Shigetomi Y, Sugiyama K, Miyagi M, Hatano T, Tajima E, Aikawa A, Ohara T, Kawamura S, Hasegawa A. Successful transplantation of a cadaveric kidney with post-infectious glomerulonephritis. Pediatr Transplant. 2000;4:56–9.
4. Randhawa PS, Minervini MI, Lombardero M, Duquesnoy R, Fung J, Shapiro R, Jordan M, Vivas C, Scantlebury V, Demetris A. Biopsy of marginal donor kidneys: correlation of histologic findings with graft dysfunction. Transplantation. 2000;69:1352–7.
5. McCall SJ, Tuttle-Newhall JE, Howell DN, Fields TA. Prognostic significance of microvascular thrombosis in donor kidney allograft biopsies. Transplantation. 2003;75:1847–52.
6. Bennett WM, Hansen KS, Houghton DC, McEvoy KM. Disseminated intravascular coagulation (DIC) in a kidney donor associated with transient recipient DIC. Am J Transplant. 2005;5:412–4.
7. Alexander JW. High-risk donors: diabetics, the elderly, and others. Transplant Proc. 1992;24:2221–2.
8. Ojo AO, Leichtman AB, Punch JD, Hanson JA, Dickinson DM, Wolfe RA, Port FK, Agodoa LY. Impact of pre-existing donor hypertension and diabetes mellitus on cadaveric renal transplant outcomes. Am J Kidney Dis. 2000;36:153–9.
9. Becker YT, Leverson GE, D'Alessandro AM, Sollinger HW, Becker BN. Diabetic kidneys can safely expand the donor pool. Transplantation. 2002;74:141–5.
10. Taub HC, Greenstein SM, Lerner SE, Schechner R, Tellis VA. Reassessment of the value of post-vascularization biopsy performed at renal transplantation: the effects of arteriosclerosis. J Urol. 1994;151:575–7.
11. Oda A, Morozumi K, Uchida K. Histological factors of 1-h biopsy influencing the delayed renal function and outcome in cadaveric renal allografts. Clin Transplant. 1999;13 Suppl 1:6–12.
12. Karpinski J, Lajoie G, Cattran D, Fenton S, Zaltzman J, Cardella C, Cole E. Outcome of kidney transplantation from high-risk donors is determined by both structure and function. Transplantation. 1999;67:1162–7.
13. Pliquett RU, Asbe-Vollkopf A, Scheuermann EH, Gröne E, Probst M, Geiger H, Hauser IA. Cholesterol-crystal embolism presenting with delayed graft function and impaired long-term function in renal transplant recipients: two case reports. J Med Case Rep. 2009;3:6839. doi:10.1186/1752-1947-3-6839.
14. Remuzzi G, Cravedi P, Perna A, Dimitrov BD, Turturro M, Locatelli G, Rigotti P, Baldan N, Beatini M, Valente U, Scalamogna M, Ruggenenti P, Dual Kidney Transplant Group. Long-term outcome of renal transplantation from older donors. N Engl J Med. 2006;354:343–52.
15. Haas M, Sis B, Racusen LC, Solez K, Glotz D, Colvin RB, Castro MC, David DS, David-Neto E, Bagnasco SM, Cendales LC, Cornell LD, Demetris AJ, Drachenberg CB, Farver CF, Farris 3rd AB, Gibson IW, Kraus E, Liapis H, Loupy A, Nickeleit V, Randhawa P, Rodriguez ER, Rush D, Smith RN, Tan CD, Wallace WD, Mengel M. Banff meeting report writing committee. Banff 2013 meeting report: inclusion of c4d-negative antibody-mediated rejection and antibody-associated arterial lesions. Am J Transplant. 2014;14:272–83. doi:10.1111/ajt.12590.
16. Sis B, Mengel M, Haas M, Colvin RB, Halloran PF, Racusen LC, Solez K, Baldwin 3rd WM, Bracamonte ER, Broecker V, Cosio F, Demetris AJ, Drachenberg C, Einecke G, Gloor J, Glotz D, Kraus E, Legendre C, Liapis H, Mannon RB, Nankivell BJ, Nickeleit V, Papadimitriou JC, Randhawa P, Regele H, Renaudin K, Rodriguez ER, Seron D, Seshan S, Suthanthiran M, Wasowska BA, Zachary A, Zeevi A. Banff'09 meeting report: antibody mediated graft deterioration and implementation of Banff working groups. Am J Transplant. 2010;10:464–71. doi:10.1111/j.1600-6143.2009.02987.x.

17. Haas M, Ratner LE, Montgomery RA. C4d staining of perioperative renal transplant biopsies. Transplantation. 2002;74:711–7.
18. Jennette JC, Heptinstall RH. Heptinstall's pathology of the kidney. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2007.
19. Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Chapman JR, Allen RD. Calcineurin inhibitor nephrotoxicity: longitudinal assessment by protocol histology. Transplantation. 2004;78:557–65.
20. Sis B, Dadras F, Khoshjou F, Cockfield S, Mihatsch MJ, Solez K. Reproducibility studies on arteriolar hyaline thickening scoring in calcineurin inhibitor-treated renal allograft recipients. Am J Transplant. 2006;6:1444–50.
21. Boubenider S, Hiesse C, Goupy C, Kriaa F, Marchand S, Charpentier B. Incidence and consequences of post-transplantation lymphoproliferative disorders. J Nephrol. 1997;10:136–45.
22. Feng S, Buell JF, Chari RS, DiMaio JM, Hanto DW. Tumors and transplantation: the 2003 third annual ASTS state-of-the-art winter symposium. Am J Transplant. 2003;3:1481–7.
23. WHO. Classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: IARC Press; 2008.
24. Rungta R, Ray DS, Das P, Gupta S. Three different opportunistic infections in the same renal allograft recipient at the same time: unusual case report. Trop J Med Res. 2014;17:45–7.
25. Weikert BC, Blumberg EA. Viral infection after renal transplantation: surveillance and management. Clin J Am Soc Nephrol. 2008;3 Suppl 2:S76–86. doi:10.2215/CJN.02900707.
26. Brennan DC. Cytomegalovirus in renal transplantation. J Am Soc Nephrol. 2001;12:848–55.
27. Freeman Jr RB. The 'indirect' effects of cytomegalovirus infection. Am J Transplant. 2009;9:2453–8. doi:10.1111/j.1600-6143.2009.02824.x.
28. Hariharan S. BK virus nephritis after renal transplantation. Kidney Int. 2006;69:655–62.
29. Parasuraman R, Zhang PL, Samarapungavan D, Rocher L, Koffron A. Severe necrotizing adenovirus tubulointerstitial nephritis in a kidney transplant recipient. Case Rep Transplant. 2013;2013:969186. doi:10.1155/2013/969186.
30. Florescu MC, Miles CD, Florescu DF. What do we know about adenovirus in renal transplantation? Nephrol Dial Transplant. 2013;28:2003–10. doi:10.1093/ndt/gft036.
31. Raghavan R, Eknoyan G. Acute interstitial nephritis – a reappraisal and update. Clin Nephrol. 2014;82:149–62.

Renal Transplantation: Postoperative Technical Complications

22

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22.1 Lymphocele

Lymphocele is a well-established complication after renal transplantation. Its incidence has been reported to range from 0.6 to 18 % in several large clinical series [1–5]. Ultrasonography has increased the possibility of detecting these fluid collections [6, 7]. Most of these are small and resolve spontaneously. On the contrary, larger lymphoceles may produce clinical symptoms such as ipsilateral leg edema, abdominal swelling, fever, and, depending on their size and location, hydronephrosis by compression or displacement of the transplant ureter or the bladder.

Although some clinical reports have shown the possibility of late development of lymphoceles [8], most of these are detected 1–3 months after transplantation (Fig. 22.1).

The treatment consists of simple aspiration, external drainage, and marsupialization of the cyst into the peritoneal cavity by standard surgical technique or laparoscopy [8–12]. Lymphoceles are present in all kidney transplant experiences, and their pathophysiology remains, at the moment, almost unknown. Many contributing factors such as extensive perivascular dissection of iliac vessels, acute rejection episodes, delayed graft function, source of kidney (cadaveric versus living related donor), use of diuretics, and steroid therapy may be involved [13–16]. Recently, retransplantation and adult polycystic disease (ADPKD) in the recipient have also been considered as adjunctive significant risk factors [17, 18]. The two main sources for lymph production are lymphatics close to the iliac vessels and those present in

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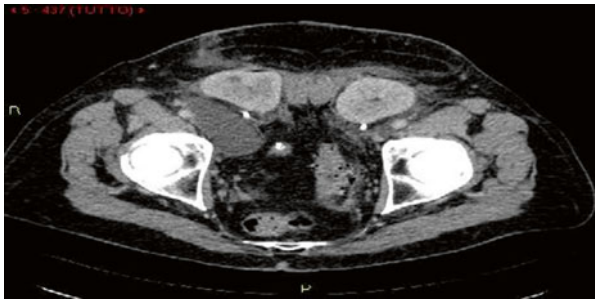

Fig. 22.1 CT scan: lymphocele near the *right* renal graft in a double kidney transplant recipient

the renal allograft ilium [13, 19, 20]. In the majority of transplant centers, including our own, the external iliac vein and artery or the hypogastric artery are used for vascular anastomoses in renal transplantation. Using this standard technique, wide dissection of perivascular lymphatic vessels is unavoidable in this region. Our opinion is that, in postrenal transplant recipients, the first step in the management of symptomatic lymphoceles should be percutaneous drainage with or without drug instillation. This will stabilize renal function and optimize patients who may require surgery and can, in itself, be curative. However, surgical marsupialization offers a superior one-step definitive treatment of lymphoceles with the lowest recurrence rates.

22.2 Posttransplant Ureteral Obstruction

Stricture of the ureterovesical junction (UVJ) anastomosis, with reported incidence rates of 2–10 %, is the most frequent urologic complication in kidney allograft recipients [21–23]. Significant stricture is a serious complication which can result in kidney failure and permanent damage to the allograft. Open surgery has traditionally been used for correction of the obstruction; however, open procedures are associated with morbidity and delayed convalescence. Development of percutaneous modalities of treatment such as percutaneous nephrostomy (PCN) with low complication rates has altered the approach to ureteral stricture. Percutaneous nephrostomy was first described by Goodwin and colleagues for temporary drainage in cases of hydronephrosis [24]. Nowadays, this procedure is widely used for the treatment of UVJ obstruction in individuals without renal replacement therapy. A number of studies have evaluated PCN in the treatment of ureteral obstruction and urine leakage in kidney transplant patients [25–27]. Ureteral obstruction and leakage are the most common urologic complications encountered in kidney transplant recipients [28–30]. Most series indicate that about 70 % of the ureteral obstructions occur within 3 months of transplantation and 80 % occur at the UVJ site [22, 31, 32]. Prompt diagnosis and early treatment are critical for preventing loss of the allograft and decreasing morbidity and mortality. Ultrasonography and renal scintigraphy can be used as initial diagnostic techniques for assessing the patency and integrity of the renal collecting system. Urinary obstruction manifests by a rising level of serum creatinine, whereas US can easily confirm the diagnosis of hydronephrosis. Diagnosis of the obstruction or leakage can be definitively confirmed using

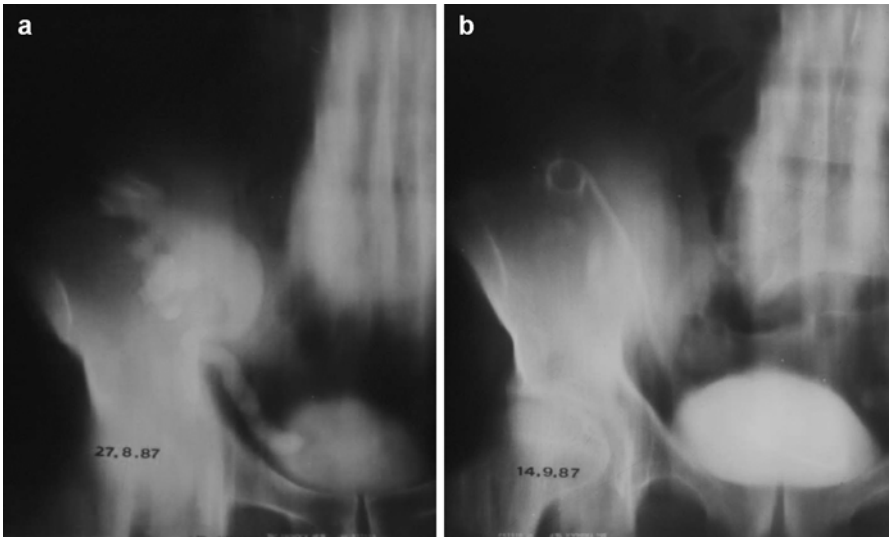

Fig. 22.2 Obstruction of the UVJ with hydronephrosis (**a**) before treatment and after placement of a ureteral stent (**b**)

percutaneous anterograde pyelography. Percutaneous approach should be considered as a method of therapy for ureteral stricture regardless of the severity of obstruction [25]. Obstructions that occur soon after transplantation are thought to be due to mechanical causes including blood clots, calculi, edema, and ischemic necrosis, whereas late obstructions are usually the result of local or generalized fibrosis due to ischemia or rejection [24, 30–34]. Fibrosis detected in late obstructions is less likely to resolve with insertion of an intraluminal ureteral stent (Fig. 22.2). As mentioned, PCN is a well-established technique for rapid relief of ureteral obstruction and improvement of the kidney function. However, if this method fails, open surgery will be considered, although it is associated with higher mortality and morbidity rates. Repeated surgery in kidney transplant patient can be extremely difficult and may result in graft loss and/or significant blood loss if not performed by an experienced surgeon.

22.3 Urinary Leakage

Leakage is usually the result of ureteral necrosis as a consequence of rejection or vascular insufficiency [33–35] and can be treated by insertion of an indwelling ureteral catheter for 21–60 days without the need for PCN or surgery. Indwelling stents may also be of use as a measure to control urinary leakage and allow stabilization of immunocompromised patients who are too ill to undergo the surgery. Extravasation of urine may occur from the renal pelvis, ureter, or ureteroneocystostomy site due to the surgical technique or ureteral ischemia and necrosis. Urinomas vary in size and usually appear in the first 2 weeks after transplantation between the renal graft and the bladder. Patients

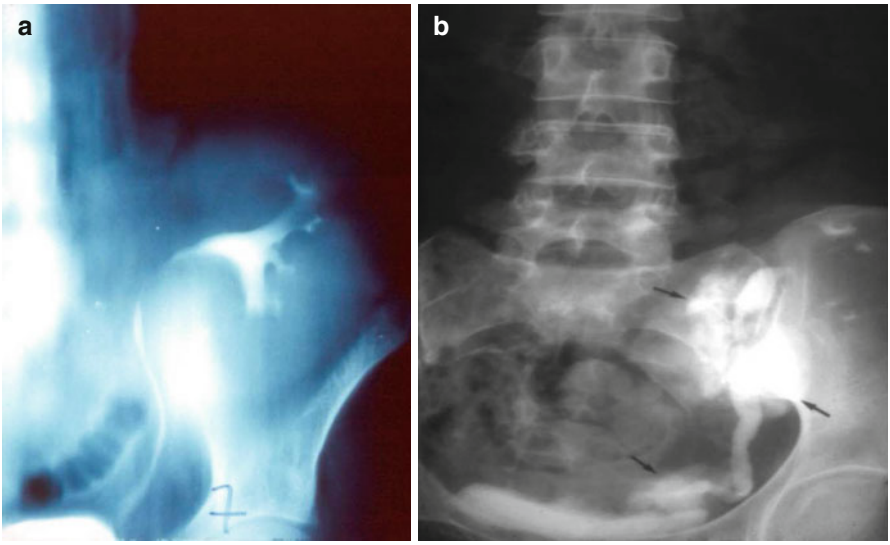

Fig. 22.3 Urinary leakage: normal anterograde pyelography (**a**) and urinary leakages (**b**)

with renal leakage may present decreased urine output and manifest pain, tenderness around the graft, discharge from the wound, or even ipsilateral leg swelling and scrotal or labial edema. On US, a urine leak or urinoma appears as an anechoic fluid collection with well-defined borders and lack of septations. Its size increases rapidly, and drainage often needs to be performed with ultrasound guidance to relieve compression and urinary ascites. The higher creatinine level of the fluid compared with its serum concentration differentiates a urine leak from seroma or lymphocele. In addition, urinomas can become infected and eventually form abscesses. Anterograde pyelography is necessary to depict the site of leak and to plan the appropriate intervention (Fig. 22.3). Small urine leaks may be treated with percutaneous nephrostomy and stent placement.

22.4 Vascular Complications

Vascular complications occur in fewer than 10 % of renal transplant recipients but are an important cause of graft dysfunction with high associated morbidity and mortality. Despite the fact that magnetic resonance angiography is superior in the diagnosis of vascular complications, color Doppler US, although conventional, remains an excellent noninvasive technique for evaluating vascular pathology [36, 37].

22.5 Renal Artery Stenosis

Transplant artery stenosis is the most common vascular complication (up to 10 %) [38–41]. It usually occurs within the first 3 months [39]. Strictures can affect the iliac artery just proximal to the anastomotic site (atherosclerotic disease in the donor vessel, surgical clamping injury), the anastomosis itself (related to surgical

technique), or the proximal renal artery (intimal ischemia). Approximately half of renal artery stenoses can be located adjacent to the anastomosis; moreover, end-to-end anastomoses have a threefold greater risk of stenosis than end-to-side anastomoses [42]. Evaluation for renal artery patency should be performed in several clinical scenarios: (a) severe hypertension refractory to medical therapy, (b) hypertension combined with an audible bruit over the graft, and (c) hypertension associated with unexplained graft dysfunction. Moderate hypertension alone is not a precise marker for renal artery stenosis because up to 65 % of transplant recipients have non-renovascular hypertension. The renal artery is mapped by using color Doppler techniques. The stenotic segments reveal focal color aliasing due to increased flow velocity. Doppler criteria for significant stenosis include the following: (a) velocities greater than 200 cm/s, (b) a velocity gradient between stenotic and prestenotic segments of more than 2:1, and (c) marked distal turbulence (spectral broadening). In the segmental artery branches of the transplant, tardus-parvus waveform abnormalities, decreased resistivity index (RI < 0.56), and loss of early systolic peak may variably be observed [41, 43–45]. Even if these findings exist, when the patient is clinically doing well, only conservative monitoring is performed [43]. When treatment is necessary, percutaneous transluminal angioplasty with or without stent placement is nowadays accepted as the initial treatment of choice [46]. Clinical success in the form of improvement or definite treatment has been reported in 73 % of patients.

22.6 Renal Vein Thrombosis

Renal vein thrombosis is an unusual posttransplant complication; it happens in <5 % of patients within the first postoperative week. Clinical presentation is similar to infarction with abrupt cessation of urinary function, swelling, and tenderness over the graft.

Renal vein thrombosis is more likely to occur following surgical difficulty with the venous anastomosis, episodes of hypovolemia, venous compression by a peritransplant collection, or slow flow secondary to rejection. On US, the kidney may be large and hypoechoic with loss of corticomedullary differentiation. Echogenic material may be seen in the renal vein. Doppler examination shows reduced or no flow in the main renal vein, and there is increased resistance on the arterial conduit, often resulting in reversed diastolic flow in the main renal artery and/or intrarenal arteries [42, 47, 48]. If thrombosis is partial, high RI may be seen [49]. Increased focal venous velocity may also be noted in partial thrombosis, kinking, and extrinsic pressure by fluid collection. However, the combination of this finding with absence of venous flow at the hilum is diagnostic for this condition, and early recognition of this pattern is crucial because the allograft may sometimes be salvaged by prompt thrombectomy.

22.7 Renal Artery Thrombosis

Thrombosis of the main renal artery occurs very rarely (<1 % of cases) in the early postoperative period and usually leads to graft loss. It may result from severe rejection, anastomotic occlusion, arterial kinking, or intimal flap. Patients with renal

transplant infarction present with anuria and often with swelling and tenderness over the graft [50].

Color Doppler imaging reveals no arterial and venous flow distal to the thrombus and in the intrarenal vessels. Similar findings can be present at severe rejection. Thrombosis of an accessory renal artery or intrarenal arterial branches will result in segmental infarcts. Although a main artery thrombosis usually results in nephrectomy, there has been some reported success with percutaneous angiographic thrombolytic techniques for treating infarcts. Early diagnosis and treatment are vital for allograft salvage [51].

References

1. Malovrh M, Kandus A, Butorovic-Ponikvar J, et al. Frequency and clinical influence of lymphoceles after kidney transplantation. Transplant Proc. 1990;22:1423–4.
2. Schweizer RT, Cho SI, Kountz SL, Belzer FO. Lymphoceles following renal transplantation. Arch Surg. 1972;104:42–5.
3. Braun WE, Banowsky LH, Straffon RA, et al. Lymphoceles associated with renal transplantation. Report of 15 cases and review of the literature. Am J Med. 1974;57:714–29.
4. Zincke H, Woods JE, Leary FJ, et al. Experience with lymphoceles after renal transplantation. Surgery. 1975;77:444–50.
5. Bear RA, McCallum RW, Cant J, et al. Perirenal lymphocyst formation in renal transplant recipients: diagnosis and pathogenesis. Urology. 1976;7:581–6.
6. Morly P, Barnett E, Belli PRF, et al. Ultrasound in the diagnosis of fluid collections following renal transplantation. Clin Radiol. 1975;26:199–207.
7. Petrek J, Tilney NL, Smith EH, et al. Ultrasound in renal transplantation. Ann Surg. 1977;185:441–7.
8. Langle F, Schurawitzki H, Muhlbacker F, et al. Treatment of lymphoceles following renal transplantation. Transplant Proc. 1990;22:1420–2.
9. Shaver TR, Swanson SJ, Fernandez-Bueno C, Kocandrle V. The optimal treatment of lymphoceles following renal transplantation. Transpl Int. 1993;6:108–10.
10. McCullough CS, Soper NJ, Clayman RV, et al. Laparoscopic drainage of a posttransplant lymphocele. Transplantation. 1991;51:725–7.
11. Ratner LE, Bender JS. A novel approach to the drainage of loculated perirenal allograft lymphoceles. Dual scope laparoscopy. Transplantation. 1994;58:961–4.
12. Khauli RB, Stoff JS, Lovewell T, et al. Post-transplant lymphoceles: a critical look into the risk factors, pathophysiology and management. J Urol. 1993;150:22–6.
13. Ward K, Klingensmith III WC, Sterioff S, Wagner HN. The origin of lymphoceles following renal transplantation. Transplantation. 1978;25:346–7.
14. Koene RA, Skotnicki SH, Debruyne FM. Spontaneous renal decapsulation with excessive fluid leakage after transplantation. NEJM. 1979;300:1030–1.
15. Madura JA, Dumbar JB, Cerilli GJ. Perirenal lymphocele as a complication of renal transplantation. Surgery. 1970;68:310–3.
16. Szwed AJ, Maxwell DR, Kleit SA, Hamburger RJ. Angiotensin II, diuretics, and thoracic duct flow in the dog. Am J Physiol. 1973;224:705–8.
17. Stephanian E, Matas AJ, Gores P, et al. Retransplantation as a risk factor for lymphocele formation. Transplantation. 1992;53:676–8.
18. Martinez-Ocana JC, Lauzurica R, Castellote E, et al. Adult polycystic kidney disease: a risk factor for lymphocele formation after renal transplantation? Transplant Proc. 1995;27:2246–7.
19. Pedersen NC, Morris B. The role of the lymphatic system in the rejection of homografts: a study of lymph from renal transplants. J Exp Med. 1970;131:936–69.

20. Howard RJ, Simmonds RL, Najarian JS. Prevention of lymphoceles following renal transplantation. Ann Surg. 1976;184:166–8.
21. Shoskes DA, Hanbury D, Cranston D, Morris PJ. Urological complications in 1,000 consecutive renal transplant recipients. J Urol. 1995;153:18–21.
22. Jones JW, Hunter DW, Matas AJ. Percutaneous treatment of ureteral strictures after renal transplantation. Transplantation. 1993;55:1193–5.
23. Lieberman SF, Keller FS, Barry JM, Rösch J. Percutaneous antegrade transluminal ureteroplasty for renal allograft ureteral stenosis. J Urol. 1982;128:122–4.
24. Goodwin WE, Casey WC, Woolf W. Percutaneous trocar (needle) nephrostomy in hydronephrosis. J Am Med Assoc. 1955;157:891–4.
25. Bhagat VJ, Gordon RL, Osorio RW, et al. Ureteral obstructions and leaks after renal transplantation: outcome of percutaneous antegrade ureteral stent placement in 44 patients. Radiology. 1998;209:159–67.
26. Swierzewski 3rd SJ, Konnak JW, Ellis JH. Treatment of renal transplant ureteral complications by percutaneous techniques. J Urol. 1993;149:986–7.
27. Alcaraz A, Bujons A, Pascual X, et al. Percutaneous management of transplant ureteral fistulae is feasible in selected cases. Transplant Proc. 2005;37:2111–4.
28. Loughlin KR, Tilney NL, Richie JP. Urologic complications in 718 renal transplant patients. Surgery. 1984;95:297–302.
29. Kinnaert P, Hall M, Janssen F, Vereerstraeten P, Toussaint C, Van Geertruyden J. Ureteral stenosis after kidney transplantation: true incidence and long-term follow up after surgical correction. J Urol. 1985;133:17–20.
30. Oosterhof GO, Hoitsma AJ, Witjes JA, Debruyne FM. Diagnosis and treatment of urological complications in kidney transplantation. Urol Int. 1992;49:99–103.
31. Schwartz BF, Chatham JR, Bretan P, Goharderakhshan R, Stoller ML. Treatment of refractory kidney transplant ureteral strictures using balloon cautery endoureterotomy. Urology. 2001;58:536–9.
32. Streem SB, Novick AC, Steinmuller DR, Zelch MG, Risius B, Geisinger MA. Long-term efficacy of ureteral dilation for transplant ureteral stenosis. J Urol. 1988;140:32–5.
33. Lojanapiwat B, Mital D, Fallon L, et al. Management of ureteral stenosis after renal transplantation. J Am Coll Surg. 1994;179:21–4.
34. Thomalla JV, Lingeman JE, Leapman SB, Filo RS. The manifestation and management of late urological complications in renal transplant recipients: use of the urological armamentarium. J Urol. 1985;134:944–8.
35. Kashi SH, Lodge JP, Giles GR, Irving HC. Ureteric complications of renal transplantation. Br J Urol. 1992;70:139–43.
36. Park SB, Kim JK, Cho KS. Complications of renal transplantation: ultrasonographic evaluation. J Ultrasound Med. 2007;26(5):615–33.
37. Parthipun A, Pilcher J. Renal transplant assessment: sonographic imaging. Ultrasound Clin. 2010;5(3):379–99.
38. Brown ED, Chen MYM, Wolfman NT, Ott DJ, Watson NE. Complications of renal transplantation: evaluation with US and radionuclide imaging. Radiographics. 2000;20(3):607–22.
39. Dodd GD, Tublin ME, Shah A, Zajko AB. Imaging of vascular complications associated with renal transplants. Am J Roentgenol. 1991;157(3):449–59.
40. Hohnke C, Abendroth D, Schleibner S, Land W. Vascular complications in 1200 kidney transplantations. Transplant Proc. 1987;19(5):3691–2.
41. Taylor KJW, Morse SS, Rigsby CM. Vascular complications in renal allografts: detection with duplex Doppler US. Radiology. 1987;162(1):31–8.
42. Jordan ML, Cook GT, Cardella CJ. Ten years of experience with vascular complications in renal transplantation. J Urol. 1982;128(4):689–92.
43. Tublin ME, Dodd GD. Sonography of renal transplantation. Radiol Clin N Am. 1995;33(3):447–59.
44. Snider JF, Hunter DW, Moradian GP, Castaneda- Zuniga WR, Letourneau JG. Transplant renal artery stenosis: evaluation with duplex sonography. Radiology. 1989;172(3):1027–30.

45. Kim SH. Vascular diseases of the kidney. In: Kim SH, editor. Radiology illustrated. Philadelphia: WB Saunders; 2003. p. 429–32.
46. Beecro JR, Rajan DK, Clark TWI, Robinette M, Stavropoulos SW. Transplant renal artery stenosis: outcome after percutaneous intervention. J Vasc Interv Radiol. 2004;15(12):1407–13.
47. Reuther G, Wanjura D, Bauer H. Acute renal vein thrombosis in renal allografts: detection with duplex Doppler US. Radiology. 1989;170(2):557–8.
48. Surlan M, Popovic P. The role of interventional radiology in management of patients with end-stage renal disease. Eur J Radiol. 2003;46:96–114.
49. Vollmer WM, Wahl PW, Blagg CR. Survival with dialysis and transplantation in patients with end-stage renal disease. N Engl J Med. 1983;308(26):1553–8.
50. Akbar SA, Jafri SZH, Amendola MA, Madrazo BL, Salem R, Bis KG. Complications of renal transplantation. Radiographics. 2005;25(5):1335–56.
51. Rouviere O, Berger P, Beziat C, et al. Acute thrombosis of renal transplant artery: graft salvage by means of intra-arterial fibrinolysis. Transplantation. 2002;73:403–9.

Part IV

Intestinal/Multivisceral Transplantation

Indications and Timing for Intestinal/ Multivisceral Transplantation

23

Loris Pironi

23.1 Introduction

Intestinal failure (IF) has been defined as a reduction in the functioning gut mass below the minimum amount necessary for adequate digestion and absorption of nutrients to achieve and maintain normal nutritional status [1]. Long-term home parenteral nutrition (HPN) is the "artificial gut" for the medical treatment of chronic IF (CIF), caused by various gastrointestinal or systemic benign diseases. CIF can be due to four pathophysiological conditions: short bowel syndrome (SBS), chronic intestinal pseudo-obstruction, small bowel parenchymal disease, and intestinal fistula [2] (Table 23.1). In Europe, the prevalence of CIF ranges from 5 to 20 cases per million population. CIF has been included in the 2013 European "Orphanet" list of rare diseases [3].

Intestinal rehabilitation programs based on medical treatment and non-transplant surgery can improve the intestinal functions and allow weaned off HPN [4]. Patients with irreversible CIF are destined to lifelong HPN or to intestinal transplantation (ITx). Published cohorts [5] showed mean 5- and 10-year survival rates on HPN of 70 and 55 % in adults and 89 and 81 % in children. HPN complications were the cause of 14 % of deaths in adults and of up to 70 % of deaths in babies <1 year [5]. The 2013 International Transplant Registry report showed a 5-year patient survival rate of 40–60 % in adults and 50–70 % in children, depending on the type of transplant with the best results after isolated small bowel ITx. Almost all the deaths after ITx were related to the treatment [6].

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Table 23.1 Pathophysiology of intestinal failure and underlying diseases of patients on long-term home parenteral nutrition

	Adults (n. 688)	Children (n. 166)
Short bowel syndrome (no. (%))	**514 (74.7 %)**	**87 (52.4 %)**
Mesenteric ischemia	36 %	
Crohn's disease	29 %	
Rx enteritis	10 %	
Surgical complications	8 %	
Familial polyposis	4 %	
Volvulus	2 %	25 %
Intestinal atresia		23 %
Intestinal malformation		19 %
Necrotizing enterocolitis		15 %
Gastroschisis		6 %
Others	11 %	12 %
Motility disorder	**124 (18.0 %)**	**38 (22.9 %)**
CIPO	56 %	71 %
Rx enteritis	16 %	
Scleroderma	6 %	
MNGIE	3 %	
Hirschsprung's disease	2 %	16 %
Others	17 %	13 %
Extensive parenchymal disease	**35 (5.1 %)**	**41 (24.7 %)**
Coeliac	17 %	
Atrophy-Ig deficiency	14 %	7 %
Crohn's disease	14 %	10 %
Lymphangiectasia	11 %	12 %
Rx enteritis	9 %	
Tufting enteropathy	6 %	24 %
Autoimmune enteropathy	6 %	7 %
Intractable diarrhea	3 %	17 %
Microvillus atrophy		10 %
Others	20 %	12 %
Intestinal fistulas	**15 (2.2 %)**	**0**
Surgical complication	60 %	
Crohn's disease	27 %	
Others	13 %	

Adapted from [2]

On the basis of data on safety and efficacy, HPN is considered the primary treatment for CIF. The indications for ITx were firstly developed by expert consensus in 2001 and could be categorized as HPN failure, high risk of death due to the underlying disease, or very poor quality of life (QoL) related to the underlying IF [2, 7, 8] (Table 23.2). Those indications were based on retrospective

Table 23.2 Five-year relative risk of death on home parenteral nutrition (HPN) reported in the European prospective survey [2, 10, 11], for each indication criteria for intestinal transplantation (ITx) as defined by the USA Medicare Services [7] and by the American Society of Transplantation position paper [8]. Proposed revision of the criteria, according to the observed results

Results of the European prospective survey on candidates for ITx [2, 10, 11]			
Indication criteria for ITx			
According to the USA Medicare Services [7] and American Society of Transplantation [8]	5-year risk of death on HPN		Proposed revision of the criteria for patient referral for ITx, according to the results of the European survey
	RR	P	
Failure of HPN			
IFALD-related liver failure: Impending (total bilirubin above 3–6 mg/dL/54–108 µmol/L, progressive thrombocytopenia, and progressive splenomegaly) or Overt liver failure (portal hypertension, hepatosplenomegaly, hepatic fibrosis or cirrhosis)	3.2	0.002	Significantly increased risk of death on HPN. Criterion for a life-saving ITx Comment: Combined liver and intestinal transplantation is a potential life-saving therapy Isolated intestinal transplant may reverse liver fibrosis or cirrhosis in adults with SBS and no signs of portal hypertension and preserved hepatic synthetic function Isolated liver transplant may be successful in children with SBS, liver failure, and portal hypertension, who have favorable prognostic features for full enteral adaptation and weaning from HPN after transplantation
CVC-related thrombosis of ≥2 central veins	2.1	0.058	Nonsignificant increased risk of death on HPN. "Borderline" criterion for a life-saving ITx, requiring a case-by-case decision Comment: Complete or impending loss of venous access has never been reported Venous access is required for the graft procedure; a delay in referral for transplant evaluation until conventional venous access is lost can prove disastrous
Frequent and severe CVC-related sepsis: 2 or more episodes per year of systemic sepsis secondary to line infections requiring hospitalization A single episode of line-related fungemia Septic shock and/or acute respiratory distress syndrome	1.1	0.929	No increased risk of death on HPN. This can be no longer a criterion for referral for ITx Comment: Sepsis is the most frequent cause of death after ITx Proper education and specific training of patients and caregivers is the most important strategy for reducing the risk of CVC-related infections. Taurolidine and ethanol locks are new promising strategies

(continued)

Table 23.2 (continued)

Results of the European prospective survey on candidates for ITx [2, 10, 11]			
Indication criteria for ITx			
According to the USA Medicare Services [7] and American Society of Transplantation [8]	5-year risk of death on HPN		Proposed revision of the criteria for patient referral for ITx, according to the results of the European survey
	RR	P	
Frequent episodes of severe dehydrations, despite intravenous fluids in addition to HPN	0		No increased risk of death on HPN. This can be no longer a criterion for referral for ITx Comment: This indication was based on the risk of chronic renal failure due to recurrent episodes of acute renal failure because of dehydration in patients with high intestinal losses of fluids and electrolytes Decrease of renal function and the risk for developing chronic renal failure are greater after ITx than during HPN
High risk of death attributable to the underlying disease			
Intra-abdominal invasive desmoid tumors	7.1	<0.001	Significantly increased risk of death on HPN. Criterion for a life-saving ITx Comment: In these patients, the need for HPN has been reported to represent a strong predictor of mortality because it mirrors the progression of the tumor
Ultra-SBS (gastrostomy, duodenostomy, residual small bowel <10 cm in infants or <20 cm in adults)	0.8	0.763	No increased risk of death on HPN. This can be no longer a criterion for a straight referral for ITx; a case-by-case decision is required Comment: This indication was based on the higher risk of IFALD-related liver failure and CVC-related sepsis in patients with an ultra-SBS, reported by earlier case series Recent improvements in intestinal rehabilitation programs have significantly decreased this risk
Congenital mucosal disorders (e.g., microvillus atrophy, intestinal epithelial dysplasia)	0.4	0.374	No increased risk of death on HPN. This can be no longer a criterion for a straight referral for ITx; a case-by-case decision is required Comment: Earlier case series reported uniformly poor outcomes associated with these mucosal enteropathies. Recent surveys showed improved outcomes, with some children successfully weaned off HPN to full oral nutrition

Table 23.2 (continued)

Results of the European prospective survey on candidates for ITx [2, 10, 11]			
Indication criteria for ITx			
According to the USA Medicare Services [7] and American Society of Transplantation [8]	5-year risk of death on HPN		Proposed revision of the criteria for patient referral for ITx, according to the results of the European survey
	RR	P	
Very poor quality of life (IF with high morbidity or low acceptance of HPN)			
Need for frequent hospitalization, narcotic dependency, or inability to function Patient's unwillingness to accept long-term home parenteral nutrition			No increased risk of death on HPN. This could be a potential criterion for a "rehabilitative ITx" in case-by-case carefully selected patients Comment: A recent comparative study clearly indicated that a successful ITx can improve the quality of life of patients with CIF destined to lifelong HPN

RR relative risk, *HPN* home parenteral nutrition, *ITx* intestinal transplantation, *IFALD* intestinal failure-associated liver disease, *CVC* central venous catheter, *SBS* short bowel syndrome, *CIF* chronic intestinal failure

analyses of national and international registries and individual center cohorts of CIF. Subsequently, there have been many advances in the management of CIF resulting in much better outcomes [4, 5, 9]. Therefore, in 2004, the Home Artificial Nutrition and Chronic Intestinal Failure working group of the European Society for Clinical Nutrition (ESPEN) carried out a 5-year prospective comparative study to evaluate their appropriateness [2, 10, 11]. Two cohorts of patients on HPN for CIF were compared: 165 candidates for ITx (108 adults, 57 children, having an indication and no contraindication for ITx) and 418 noncandidates (322 adults, 96 children, having neither an indication nor a contraindication for ITx). The 5-year survival rate on HPN was 87 % in noncandidates, 74 % in candidates with HPN failure, 84 % in those with high-risk underlying disease, and 100 % in those with high-morbidity IF/low acceptance of HPN. The analysis of the risk of death and the causes of death on HPN associated with each indication showed that only patients with liver failure due to intestinal failure-associated liver disease (IFALD) or invasive intra-abdominal desmoids had an actual increased risk of death on HPN. In these patients, almost all (91.7 %) of deaths on HPN were related to an indication for ITx. On the contrary, none of the other indications for ITx showed a statistically significant increased risk of death on HPN, and only 35.8 % of deaths occurred in patients with these indications were related to the underlying disease or to HPN. The European survey suggested a revision of the referral criteria for ITx [5, 11].

23.2 Proposed Revision of the Indications for ITx, According to the Results of the European Survey [2, 5, 10, 11] (Table 23.2)

Liver failure due to IFALD showed a statistically significant increased risk of death on HPN and was confirmed as a referral criterion for a life-saving ITx. Abnormalities of liver function tests (LFTs) have been reported at a frequency of between 15 and 85 % of patients on HPN [12, 13]. Chronic cholestasis with inflammation and rapid progression to fibrosis, portal hypertension, and end-stage liver disease is the predominant histologic feature in neonates and infants <6 months, whereas steatosis and steatohepatitis with a slower evolution to fibrosis are the principal lesions in older children and adults [14]. In 22 adult case series and 16 children cohorts, IFALD-related death represented the 4–5 % and the 16–60 % of total death on HPN, respectively, with a mortality rate greater in premature infants and in babies [5].

The pathogenesis of IFALD is multifactorial [5, 12, 13]. Total oral fasting and very short bowel syndrome (SBS) are the main IF-related factors. The main HPN-related factors consist of excess total energy, excess glucose, or excess soybean-based lipid emulsions (LE) (>1 g/Kg body weight/day in adults and >2.5 g/Kg/day in children), rich in proinflammatory omega-6 polyunsaturated fatty acids, even without hyperalimentation [30, 31]. Other potential HPN factors may be excess phytosterols in LE and antioxidant deficiency, like vitamin E. A key role has been demonstrated for the systemic or intra-abdominal inflammation, notably through sepsis – of whatever origin – or intestinal bacterial translocation [5, 12–16].

In the recent years, prevention and treatment of IFALD have improved allowing to avoid the need for ITx in a consistent number of patients [4]. The main strategies aim to maintain oral feeding, to decrease the risk of central venous catheter (CVC)-related sepsis, and to decrease the amount of soybean-based LE, or its replacement with fish oil-based LE, containing the anti-inflammatory omega-3 polyunsaturated fatty acids as well as higher amount of vitamin E and lower concentration of phytosterols, would be recommended [16, 18].

When medical treatment fails, the issues of *patient referral for transplantation*, *type of transplantation,* and *timing of transplantation* arise. According to a severity classification of IFALD proposed in 2008 [19], persistent hyperbilirubinemia from 3 to 6 mg/dL (50–100 μmol/L) would be a criterion for *referral to intestinal failure rehabilitation unit* and persistent concentration >6 g/dL a criterion for consultation or *referral for transplantation assessment and listing*. Knowing when hepatic fibrosis is progressing up to irreversible cirrhosis is a key issue for the timing for referral as well as for the type of transplantation. LFTs do not predict the degree of histological injury [14]. A recent study [17] in adults found that the FibroScan® score, a noninvasive marker of liver fibrosis in various liver diseases, was significantly correlated with the histological score of cholestasis but not of fibrosis. Therefore, serial liver biopsy remains the gold standard for assessing IFALD.

The Intestinal Transplant Registry shows that *combined liver and ITx*, either small bowel alone or multivisceral, have the same patient survival probability of ITx without liver, but a higher probability of graft survival. Fiel et al. reported the

decrease of liver fibrosis in four adult patients [20] and reversal of cirrhosis in another patient [21] after successful engraftment of an *isolated ITx*. All the patients had an *S*BS, preserved hepatic synthetic function, and absence of portal hypertension [20, 21]. The regression of fibrosis might in part be due to the improved portal blood flow that occurs with a new intestinal allograft or to the IF-associated portal endotoxemia. No similar data have yet been reported in children.

It has been shown that *isolated liver transplant* (iLTx) may be successful with long-term survival in children with liver failure and portal hypertension as a result of SBS, who have favorable prognostic features for full enteral adaptation and weaning from HPN after transplantation [22, 23]. After iLTx, intestinal function may improve because the degree of portal hypertension and bowel edema might contribute to the pretransplant intolerance to enteral feeds. The following criteria for iLTx in children with SBS and liver failure have been suggested [23]: (a) serum bilirubin >200 μmol/L, moderate/severe fibrosis, and portal hypertension; (b) ≥50 cm of intact functional small bowel without an ICV or 30 cm with an ICV; (c) ≥50 % of the estimated daily energy requirement tolerated as enteral feeds for at least 4 weeks before the development of liver disease and associated with an increase in weight; and (d) minimal CVC infections (<6/12 months). If these criteria would be applicable to adults as well is not known.

Once patients have been listed, the *priority criteria for* combined liver-ITx are a matter of debate. Stratification of waiting times for liver-ITx was regulated by the models for adult and pediatric end-stage liver disease (MELD and PELD). However, deaths on the waiting list for combined liver-ITx were eight times higher compared to iLTx without IF [24]. As a result these scores were adjusted to incorporate a sliding scale of 10 % mortality at 3 months. Over time this has reduced time waiting for a transplant, increased the number of liver-ITx, and narrowed the gap between the two groups in both pediatric and adult populations [25]. In addition, the MELD score and C-reactive protein have been shown to be independent predictors of survival and may be considered as reasons for early transplantation [26].

The *occlusion of greater than or equal to two central veins* due to CVC-related thrombosis resulted in a "borderline," non-statistically significant increased risk of death on HPN. This implies that this should not to be considered a criterion for a patient straight referral for a life-saving ITx and that a case-by-case decision would be the preferred strategy. The incidence of CVC-related thrombosis is quite low (0.02–0.09 per catheter year), with the highest rates reported in children [5]. The mortality is very rare (0–3.9 %) and becomes a substantial risk only in those patients with a vena cava syndrome (6.8 %) [5]. Although true complete or impending loss of venous access has never been reported, the loss of venous access is an important concern, because access is required for the graft procedure, so a delay in referral for ITx evaluation until conventional venous access is lost can prove disastrous [5, 27].

The European survey showed no increased risk of death on HPN associated with *frequent and severe episodes of CVC-related sepsis*. Considering also that sepsis is the most frequent cause of death after ITx [6], CVC-related infections should no longer be considered an indication for ITx. The incidence of CVC-related infection has been reported to range between 0.38 and 4.58 episodes per 1,000 catheter days

with a median of 1.31 [28] with an associated death rate to 8 % in adults and 30 % in children [5]. Proper education and specific training of staff is universally recommended as the most important and evidence-based strategy for reducing the risk of this complication [13, 28, 29]. The use of taurolidine or ethanol locks as well as HPN infusion via an arteriovenous fistula has been reported to further decrease CVC-related infections [5].

Frequent episodes of severe dehydration despite intravenous fluids in addition to HPN were a criterion for referral for ITx in only two patients of the European survey. This complication usually occurs in patients with high intestinal losses of fluids, as those with an SBS and an end jejunostomy. Severe dehydration may cause an acute renal failure (ARF) that generally resolves after appropriate intravenous hydration. The rationale for this indication for ITx was the risk of chronic renal failure (CRF) that may arise after repeated episodes of ARF. A decrease of glomerular filtration rate (GFR) may occur in about 50 % of patients after many years of HPN [30, 31]. However, ITx is the organ transplant at the highest risk for patients to develop CRF, with a 21 % incidence at 5-year post-ITx [32]. The prevalence and the probability of CRF on HPN and after ITx were recently compared [33]. After a median of 7 years of treatment, the frequency of CRF was 21 % in HPN patients and 54 % in ITx recipients, with an annual decline of GFR of 2.8 % and 14.5 %, respectively. The 5-year probability of maintaining a GFR ≥60 ml/min was 84 % in the HPN group and 44 % in the ITx group [33]. These data definitively indicate that frequent and severe episodes of dehydration on HPN, as a criterion for ITx, should be abandoned.

The European survey showed that also patients who were on HPN because of *invasive intra-abdominal desmoids* had a significantly increased risk of death and were therefore candidates for a life-saving ITx. Quintini et al. showed that in these patients, survival rate was negatively affected by the presence of pain, the dimension of the tumor (e.g., >10 cm), and the requirement for long-term HPN [34]. Even though the duration of HPN did not affect mortality, the need for HPN represented a strong predictor of mortality and represented an independent poor prognostic factor associated with high morbidity and mortality. ITx would offer the advantages of making the removal of the tumor easier and more complete and is a potentially life-saving therapy for early referred patients [35].

Children with CIF due to *congenital mucosal disorders* (e.g., microvillus atrophy, intestinal epithelial dysplasia) did not show a 5-year increased risk of death on HPN. In earlier case series mucosal enteropathies were reported to be associated with uniformly poor outcomes [5]. Recent studies showed improved outcomes, with some children successfully weaned off HPN [36, 37]. These data clearly indicate that congenital mucosal disorders are no longer a criterion for a straight referral for a life-saving ITx.

Also the presence of an *ultra-SBS* was not associated with an increased risk of death on HPN and should no longer be a criterion for a life-saving ITx. Earlier case series showed an increased risk of death due to IFALD and CVC-related sepsis in the presence of a small bowel remnant <50 cm in adults and <15 % of the expected normal length in infants and children [5, 38, 39]. The improvements in intestinal

rehabilitation programs have decreased the frequency and the severity of these two major HPN-related complications and have increased the survival rate of these patients [5, 40, 41].

The results of the European survey showed a 100 % 5-year survival rate in candidates for ITx because of a *very poor QoL* due to CIF with high morbidity or low acceptance of HPN.

Adult patients experiencing an acute onset of IF may negatively react to the prospect of long-term HPN, but an improvement of the QoL has been reported with the improvement of nutritional status due to HPN, in patients having severe malnutrition as the result of chronic and devastating gastrointestinal diseases [42, 43]. Furthermore, a better QoL in patients on long-term HPN compared with those on short-term HPN has been reported, indicating an adaptation with time [42, 43]. In adults, a poor QoL on HPN has been reported to be due to not eating or drinking normally, loss of independence with limitation in social life, change in social status, implications for the financial status, worsening nutritional status, increased number of HPN infusions per week, frequency of nocturnal urination, and need of opiates to control pain [42, 43]. Recently, the QoL of patients on HPN and of ITx recipients was investigated using comparable questionnaires. The results showed that ITx recipients had a better score in the ability to holiday/travel, fatigue, gastrointestinal symptoms, stoma management/bowel movements, and global health status/quality of life, indicating that a successful ITx can improve the QoL of patients with CIF [44]. Overall, these results would support a rehabilitative role of ITx for patients with irreversible CIF and very poor QoL, but the above reported data on the survival rate do not yet allow to consider this a criterion for a straight referral for ITx.

23.3 Issues with a Potential Indication for a Rehabilitative ITx

In the European survey, the 5-year survival rate of the candidates designated because of CVC-related complications or ultrashort bowel did not differ between those who remained on HPN (83 %) and those who underwent ITx (78 %), the latter being similar to the results obtained by the most experienced US transplant centers [5, 11]. These data would implicate a potential "rehabilitative role" of ITx, to be offered on a case-by-case basis, to carefully selected patients, in order to avoid the risk of premature death following an ITx.

The information to be given to patients asking for a rehabilitative ITx should consider the survival rate, the safety, the efficacy, the QoL of both HPN and ITx, as well as the timing of referral in order to have the highest probability of a successful ITx. Survival probability is higher, and morbidity rate is lower on HPN than after ITx [5]. Considering the efficacy, in about 20 % of ITx recipients, a graft failure occurs, requiring intravenous hydration and HPN, or retransplantation may occur [6]. On the other hand, the QoL would be better after successful ITx than on HPN [44]. The timing of patient referral for ITx is a key factor for the probability of survival after ITx, because a late referral is associated with an increased risk of death. The survival rate is higher in patients who are in good clinical status at time of

calling for the transplantation [6, 24]. Adult candidates after the fourth decade have a decreased survival probability [5, 6, 45].

23.4 Conclusions

The progress in intestinal rehabilitation therapy has modified the strategy of treatment of CIF, moving from a straight referral for ITx of any patients with a potential risk of death on HPN to the early referral of patients to intestinal rehabilitation centers with expertise in both medical and surgical treatment for CIF, in order to maximize the opportunity of weaning off HPN, to prevent HPN failure, and to ensure timely ITx when this is needed [19].

Recent data indicate that only liver failure due to IFALD and invasive intra-abdominal desmoids are the criteria for a straight referral for ITx. CVC-related thrombosis of greater than or equal to two central veins could be also considered for a life-saving ITx, in appropriately selected patients. For patients having none of the above criteria, ITx might have a potential rehabilitative role, but a careful decision must be taken on a case-by-case basis for adequately informed patients.

References

1. Fleming CR, Remington M. Intestinal failure. In: Hill GI, editor. Nutrition and the surgical patient. Edinburgh: Churchill Livingston; 1981. p. 219–35.
2. Pironi L, Hébuterne X, Van Gossum A, Messing B, Lyszkowska M, Colomb V, et al. Candidates for intestinal transplantation: a multicenter survey in Europe. Am J Gastroenterol. 2006;101:1633–43.
3. http://www.orpha.net/consor/cgi-bin/index.php?lng=EN.
4. Shatnawei A, Parekh NR, Rhoda KM, Speerhas R, Stafford J, Dasari V, et al. Intestinal failure management at the Cleveland clinic. Arch Surg. 2010;145:521–7. doi:10.1001/archsurg.2010.103.
5. Pironi L, Goulet O, Buchman A, Messing B, Gabe S, Candusso M, et al. Outcome on home parenteral nutrition for benign intestinal failure: a review of the literature and benchmarking with the European prospective survey of ESPEN. Clin Nutr. 2012;31:831–45. doi:10.1016/j.clnu.2012.05.004.
6. Grant D, editor. Intestinal transplant registry. ITR 2013 bi-annual report. Toronto: Intestinal Transplant Association; 2014. https://www.tts.org/ita
7. Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. Gastroenterology. 2003;124:1111–34.
8. Kaufman SS, Atkinson JB, Bianchi A, Goulet OJ, Grant D, Langnas AN, American Society of Transplantation, et al. Indications for pediatric intestinal transplantation: a position paper of the American Society of Transplantation. Pediatr Transplant. 2001;5:80–7.
9. Sigalet D, Boctor D, Brindle M, Lam V, Robertson M. Elements of successful intestinal rehabilitation. J Pediatr Surg. 2011;46:150–6. doi:10.1016/j.jpedsurg.2010.09.083.
10. Pironi L, Forbes A, Joly F, Colomb V, Lyszkowska M, Van Gossum A, et al. Survival of patients identified as candidates for intestinal transplantation: a 3-year prospective follow-up. Gastroenterology. 2008;135:61–71. doi:10.1053/j.gastro.2008.03.043.
11. Pironi L, Joly F, Forbes A, Colomb V, Lyszkowska M, Baxter J, et al. Long-term follow-up of patients on home parenteral nutrition in Europe: implications for intestinal transplantation. Gut. 2011;60:17–25. doi:10.1136/gut.2010.223255.

12. Buchman AL, Iyer K, Fryer J. Parenteral nutrition-associated liver disease and the role of isolated intestine and intestine/liver transplantation. Hepatology. 2006;43:9–19.
13. Staun M, Pironi L, Bozzetti F, Baxter J, Forbes A, Joly F, et al. ESPEN guidelines on parenteral nutrition: home parenteral nutrition (HPN) in adult patients. Clin Nutr. 2009;28:467–79. doi:10.1016/j.clnu.2009.04.001.
14. Naini BV, Lassman CR. Total parenteral nutrition therapy and liver injury: a histopathologic study with clinical correlation. Hum Pathol. 2012;43:826–33. doi:10.1016/j.humpath.2011.07.008.
15. Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med. 2000;132:525–32.
16. Diamond IR, de Silva NT, Tomlinson GA, Pencharz PB, Feldman BM, Moore AM, et al. The role of parenteral lipids in the development of advanced intestinal failure-associated liver disease in infants: a multiple-variable analysis. JPEN J Parenter Enteral Nutr. 2011;35:596–602. doi:10.1177/0148607111413598.
17. Van Gossum A, Pironi L, Messing B, Moreno C, Colecchia A, D'Errico A, et al. Transient elastography (FibroScan) is not correlated with liver fibrosis but with cholestasis in patients with long-term home parenteral nutrition. JPEN J Parenter Enteral Nutr. 2014; pii: 0148607114538057. [Epub ahead of print] PubMed PMID: 24913657.
18. Seida JC, Mager DR, Hartling L, Vandermeer B, Turner JM. Parenteral ω-3 fatty acid lipid emulsions for children with intestinal failure and other conditions: a systematic review. JPEN J Parenter Enteral Nutr. 2013;37:44–55. doi:10.1177/0148607112450300. 55.
19. Beath S, Pironi L, Gabe S, Horslen S, Sudan D, Mazeriegos G, et al. Collaborative strategies to reduce mortality and morbidity in patients with chronic intestinal failure including those who are referred for small bowel transplantation. Transplantation. 2008;85:1378–84. doi:10.1097/TP.0b013e31816dd513.
20. Fiel MI, Sauter B, Wu HS, Rodriguez-Laiz G, Gondolesi G, Iyer K, et al. Regression of hepatic fibrosis after intestinal transplantation in total parenteral nutrition liver disease. Clin Gastroenterol Hepatol. 2008;6:926–33. doi:10.1016/j.cgh.2008.04.011.
21. Fiel MI, Wu HS, Iyer K, Rodriguez-Laiz G, Schiano TD. Rapid reversal of parenteral-nutrition-associated cirrhosis following isolated intestinal transplantation. J Gastrointest Surg. 2009;13:1717–23. doi:10.1007/s11605-009-0914-7.
22. Botha JF, Grant WJ, Torres C, Iverson AK, Sudan DL, Shaw Jr BW, et al. Isolated liver transplantation in infants with end-stage liver disease due to short bowel syndrome. Liver Transpl. 2006;12:1062–6.
23. Dell-Olio D, Beath SV, de Ville de Goyet J, Clarke S, Davies P, Lloyd C, et al. Isolated liver transplant in infants with short bowel syndrome: insights into outcomes and prognostic factors. J Pediatr Gastroenterol Nutr. 2009;48:334–40.
24. Fishbein TM. Intestinal transplantation. N Engl J Med. 2009;361:998–1008.
25. Kaplan J, Han L, Halgrimson W, Wang E, Fryer J. The impact of MELD/PELD revisions on the mortality of liver-intestine transplantation candidates. Am J Transplant. 2011;11:1896–904. doi:10.1111/j.1600-6143.2011.03628.x.
26. Putchakayala K, Polensky S, Fitzhugh J, Cohran V, Buchman A, Fryer J. An evaluation of the model for end-stage liver disease and serum C-reactive protein as prognostic markers in intestinal failure patients on parenteral nutrition. JPEN J Parenter Enteral Nutr. 2009;33:55–61. doi:10.1177/0148607108322395.
27. Rodrigues AF, van Mourik ID, Sharif K, Barron DJ, de Giovanni JV, Bennett J, et al. Management of end-stage central venous access in children referred for possible small bowel transplantation. J Pediatr Gastroenterol Nutr. 2006;42:427–33.
28. Dreesen M, Foulon V, Spriet I, Goossens GA, Hiele M, De Pourcq L, et al. Epidemiology of catheter-related infections in adult patients receiving home parenteral nutrition: a systematic review. Clin Nutr. 2013;32:16–26. doi:10.1016/j.clnu.2012.08.004.
29. Buchman AL, Moukarzel A, Goodson B, Herzog F, Pollack P, Reyen L, et al. Catheter-related infections associated with home parenteral nutrition and predictive factors for the need for catheter removal in their treatment. JPEN J Parenter Enteral Nutr. 1994;18:297–302.

30. Buchman AL, Moukarzel A, Ament ME, Gornbein J, Goodson B, Carlson C, et al. Serious renal impairment is associated with long-term parenteral nutrition. JPEN Parenter Enter Nutr. 1993;17:438–44.
31. Lauverjat M, Hadj Aissa A, Vanhems P, Bouletreau P, Fouque D, Chambrier C, et al. Chronic dehydration may impair renal function in patients with chronic intestinal failure on long-term parenteral nutrition. Clin Nutr. 2006;25:75–81.
32. Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med. 2003;349:931–40.
33. Pironi L, Lauro A, Soverini V, Zanfi C, Agostini F, Guidetti M, et al. Renal function in patients on long-term home parenteral nutrition and in intestinal transplant recipients. Nutrition. 2014. doi:10.1016/j.nut.2014.02.001.
34. Quintini C, Ward G, Shatnawei A, Xhaja X, Hashimoto K, Steiger E, et al. Mortality of intra-abdominal desmoid tumors in patients with familial adenomatous polyposis: a single center review of 154 patients. Ann Surg. 2012;255:511–6. doi:10.1097/SLA.0b013e31824682d4.
35. Shatnawei A, Habib M, Hamilton C, Steiger E, Kirby DF, Speerhas R, et al. The association between home parenteral nutrition and patients with FAP-associated intra-abdominal desmoids: a retrospective study. JPEN J Parenter Enteral Nutr. 2013;37:683–8. doi:10.1177/0148607112471860.
36. Lemale J, Coulomb A, Dubern B, Boudjemaa S, Viola S, Josset P, et al. Intractable diarrhea with tufting enteropathy: a favorable outcome is possible. J Pediatr Gastroenterol Nutr. 2011;52:734–9. doi:10.1097/MPG.0b013e31820731db.
37. Halac U, Lacaille F, Joly F, Hugot JP, Talbotec C, Colomb V, et al. Microvillous inclusion disease: how to improve the prognosis of a severe congenital enterocyte disorder. J Pediatr Gastroenterol Nutr. 2011;52:460–5. doi:10.1097/MPG.0b013e3181fb4559.
38. Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud JC, Matuchansky C. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology. 1999;117:1043–50.
39. Spencer AU, Kovacevich D, McKinney-Barnett M, Hair D, Canham J, Maksym C, et al. Pediatric short-bowel syndrome: the cost of comprehensive care. Am J Clin Nutr. 2008;88:1552–9. doi:10.3945/ajcn.2008.26007.
40. Sanchez SE, Javid PJ, Healey PJ, Reyes J, Horslen SP. Ultrashort bowel syndrome in children. J Pediatr Gastroenterol Nutr. 2013;56:36–9. doi:10.1097/MPG.0b013e318266245f.
41. Torres C, Sudan D, Vanderhoof J, Grant W, Botha J, Raynor S, Langnas A. Role of an intestinal rehabilitation program in the treatment of advanced intestinal failure. J Pediatr Gastroenterol Nutr. 2007;45:204–12.
42. Baxter JP, Fayers PM, McKinlay AW. A review of the quality of life of adult patients treated with long-term parenteral nutrition. Clin Nutr. 2006;25:543–53.
43. Winkler MF. Quality of life in adult home parenteral nutrition patients. JPEN J Parenter Enteral Nutr. 2005;29:162–70.
44. Pironi L, Baxter JP, Lauro A, Guidetti M, Agostini F, Zanfi C, Pinna AD. Assessment of quality of life on home parenteral nutrition and after intestinal transplantation using treatment-specific questionnaires. Am J Transplant. 2012;12 Suppl 4:S60–6.
45. Abu-Elmagd KM, Kosmach-Park B, Costa G, Zenati M, Martin L, Koritsky DA, et al. Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation. Ann Surg. 2012;256(3):494–508. doi:10.1097/SLA.0b013e318265f310.

Intestinal/Multivisceral Transplantation: The Donor Procurement

24

Antonio D. Pinna and Chiara Zanfi

24.1 Introduction

Multiple organ procurement is a single surgical operation. It takes place constantly under urgent conditions and involves multiple surgical teams, each devoted to the retrieval of a specific organ and therefore mostly concerned with preserving their organ(s) of interest. Time for organization is usually limited, and the procedure can rarely be delayed without the risk of losing the donor or compromising the quality of the organs. For successful transplantation of each donated organ from the same donor, coordination among the surgical teams from different transplant centers is essential. Because of possible variations in techniques for the procurement of organs among transplant centers, the surgical teams should discuss the method and the estimated duration of the procedure before beginning the operation, so that each organ is optimally procured without unnecessary ischemia or injury. Organs are removed according to their susceptibility to ischemia and the need for their life-supporting or life-enhancing nature. Thus the heart or the heart and lungs are usually removed first, then the liver, the pancreas and the small bowel or the multivisceral graft, and finally the kidneys. In the past, it was suggested that the pancreas and small bowel cannot be obtained from the same cadaveric donor, particularly if the liver is also to be transplanted. The argument was that because the three organs share an axial blood supply, they cannot all be assured of an adequate blood supply when detached from each other and transplanted individually. Contrary to this assumption, it has been extensively demonstrated that the procurement of each

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abdominal organ is technically feasible and safe for transplantation [1]. The complete multivisceral specimen is envisioned as a grape cluster with a double central stem consisting of the celiac axis and superior mesenteric artery. The grapes, or individual organs, can be removed or retained according to the surgical objectives, but both arterial stem structures are preserved except when only the intestine is to be transplanted. The venous outflow from the grape cluster is entirely hepatofugal and is also kept intact up to or beyond the liver.

24.2 Donor Evaluation

Intestinal transplant recipients often undergo several previous laparotomies, leading to loss of domain of the abdomen in the abdominal cavity which often becomes a virtual space. For this reason, after an intestinal transplant procedure, the immediate closure of the abdominal incision is not always feasible. Donor-recipient size mismatch can preclude a primary abdominal closure. An acceptable donor-to-recipient body weight ratio is reported as being between 1.1 and 0.76; donor-recipient matching should take into account not only the small size of the recipient, but also the loss of domain of the abdomen in the abdominal cavity, which may result in prolonged waiting time for transplant and a possible increase in mortality and morbidity [2].

Suitable intestinal/MV donors are considered if they have a satisfactory past medical history and a stable hemodynamic condition and are receiving minimal or no intravenous doses of vasopressors, with normal levels of blood sugars and serum lipases and with normal results of liver function tests. Patients with acute brain stem injury often develop hyperglycemia due to intravenous glucose-containing crystalloid infusions: elevated serum glucose alone is not necessarily a contraindication for donation. Although more than 2,300 intestinal transplantations have been performed worldwide, a description of intestinal donor criteria is still not available; a review of the literature shows no specific report on donor profile. The most commonly cited donor criterion is age which must range between 0 and 50 years; other criteria for intestinal graft donation include ICU stay <1 week and no blunt abdominal trauma [3]. ABO blood group must be usually identical; human leukocyte antigen matching with the recipients can be random.

Selective gut decontamination must be attempted in all donors with a nonabsorbable antibiotic preparation (amphotericin B, tobramycin/gentamicin, and polymyxin E) administered through a nasogastric tube without lavage soon after acceptance into donorship and again at the time of donor surgery. In addition, standard intravenous antibiotic prophylaxis must be instituted [4]. Originally, the grafts were altered with irradiation and/or antilymphoid antibody treatment or other modalities before or after interruption of their blood flow [5].

After a complete midline incision of the chest and abdomen, the organs must be inspected in order to detect any vascular anatomical variants; the small bowel is evaluated for ischemia, edema, pulsatility, and peristalsis, and the mesentery is inspected for hematomas or injuries. The long incision provides good exposure for removal of all thoracic and abdominal viscera.

The presence of Meckel or other types of diverticulosis are acceptable.

In all cases, if the heart is procured, the aorta is encircled proximally near the diaphragm for later cross-clamping when circulation is discontinued. The distal part of the aorta is cleaned and encircled at or below the origin of the inferior mesenteric artery for insertion of the cannula for cold preservation fluid. As soon as the proximal aorta is cross-clamped, in situ perfusion is begun, and the venous beds are decompressed by venotomy of the suprahepatic vena cava [6].

24.3 Surgical Technique

24.3.1 Isolated Intestinal Graft: Donor Procedure

The isolated intestinal graft can be harvested simultaneously with all the other organs without jeopardizing the function after reperfusion of the other abdominal organs including the pancreas.

Cattel and Kocher maneuvers are performed together in order to expose the left renal vein clearly: above the vein, the superior mesenteric artery (SMA) rises from the aorta (Fig. 24.1), and the presence of an aberrant right hepatic branch needs to be excluded (the origin of the inferior pancreaticoduodenal artery must be preserved in the case of pancreas harvesting, so the SMA must be isolated up to the first jejunal vessels in order to be cut there).

The gastrocolic ligament is then divided between the stomach and transverse colon up to the splenic flexure, looking inside for the middle colic vein: following it, the superior mesenteric vein (SMV) can be reached and isolated as far as the splenomesenteric confluence into the portal vein (the origin of the inferior pancreaticoduodenal vein must be preserved in the case of pancreas harvesting, so the SMV must be isolated up to the first jejunal vessels in order to be cut there, saving the middle colic vein). The Treitz ligament can be cut now.

The proximal part of the first jejunal loop is encircled and transected with a GIA 75 stapler in order to obtain the proximal part of the graft.

On the anatomical left side of the middle colic vessels which are going to be preserved the transverse colon is encircled and transected with a GIA 75 stapler in order to obtain the distal part of the graft. The colon is necessary to orientate the graft and can sometimes be used with the graft in order to improve electrolyte and fluid balance of the recipient, but is highly immunogenic and can be responsible for posttransplantation lymphoproliferative disorder. The warm phase can be concluded separating the mesenterium from the body ligating small lymphatic and vascular vessels, in order to progress to the cold phase with the bowel connected to the body by the superior mesenteric vessels only.

After heparinization and cross-clamping and venting maneuvers, cold perfusion is performed giving an average infusion volume of 50–100 mL/Kg, carefully watching the intestine as it blanches homogeneously. Ice must be put on the towel, wrapped around the small bowel to avoid burns. Notably, cold perfusion reaches the small bowel through the SMA only (the inferior mesenteric artery is usually tied), and vein drainage is ensured by the SMV through the portal vein.

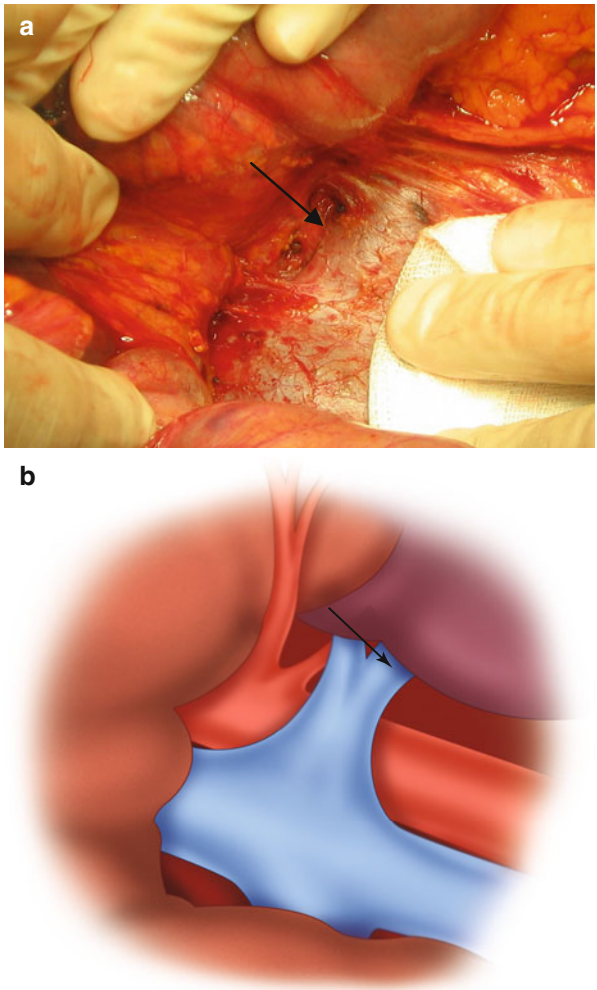

Fig. 24.1 (**a**) Above the left renal vein, the isolated superior mesenteric artery (*arrow*) arises from the aorta; (**b**) schematic representation

After liver harvesting and without pancreas procurement, the pancreatic head en bloc with the duodenum is separated from the SMV and SMA, starting from the pancreatic head (cut previously by liver surgeons) and going towards the right anatomical direction: during this maneuver small head pancreatic veins must be tied. With pancreas harvesting, the pancreaticoduodenal block must be removed from the mesenterium, keeping the superior mesenteric artery and vein small cuffs with the inferior pancreaticoduodenal vessels with the pancreas.

Finally, the SMA is cut at the aortic origin (above the right branch if present or above the inferior pancreaticoduodenal artery in the event of pancreas harvesting), and the SMV is cut at the splenomesenteric confluence (or above the inferior pancreaticoduodenal vein in the event of pancreas harvesting), putting a monofilament stitch on the anterior wall (or corner) of the vessels for orientation. Enterectomy is then completed, and perfusion of the bowel with cold perfusion is performed through the SMA.

A good suggestion is to perfuse all the abdominal viscera, at the end of the warm phase, only from the aorta, thus avoiding perfusion of the liver from the inferior mesenteric vein to prevent high outflow pressure into the superior mesenteric vein. In cadaveric donors the superior mesenteric artery is cut proximally to the middle colic artery, and the superior mesenteric vein is cut centrally to the emergence of the first jejunal vein. Care must be taken to avoid traction on the delicate jejunal veins.

The isolated intestinal graft after harvesting includes the entire small bowel and the right colon with the stump of the superior mesenteric artery and the superior mesenteric vein. At the back-table care must be taken in suturing the large lymphatic vessels around the mesenteric artery and to provide good hemostasis; bleeding from the mesentery around the SMA after reperfusion can be difficult, and excessive traction on the mesentery can cause tearing of the first jejunal veins. A modification of the isolated intestinal transplant together with the pancreas en bloc has recently been described. The major difference is that the small bowel is harvested en bloc with the duodenum and pancreas. The superior mesenteric artery is harvested possibly with an aortic patch, and the splenic artery is anastomosed to a Y-iliac graft together with the superior mesenteric artery. The donor iliac artery will then be implanted end-to-side to the aorta. The venous outflow of the entire composite graft is constituted by the portal vein, and venous reconstruction will be performed with an end-to-end anastomosis between the donor and recipient's portal vein [7].

24.3.2 Combined Liver-Intestine Graft: Donor Procedure

After cross-clamping, all the celomatic organs in the donor should be perfused only through the aorta. After harvesting of the liver en bloc with gastro-pancreatic-intestinal viscera, the donor surgeon performs the total pancreatectomy together with gastrectomy and duodenectomy at the back-table. Of course the total pancreatectomy and gastrectomy of the donor can be performed before cross-clamping, but in this case the procedure can be time-consuming, can cause blood loss, and can become dangerous for the subsequent function of the liver and intestinal grafts. At the end of the donor and back-table procedures, the composite allograft should consist of the liver with the inferior vena cava and the bile duct cut at the usual level as in the isolated liver harvesting procedure. The liver remains connected to the small bowel plus the right colon through the portal vein which is intact. The arterial vascular supply of the composite graft is through the hepatic artery and superior mesenteric artery which are kept connected if possible with an aortic patch surrounding the takeoff of the celiac axis and SMA.

24.3.3 Multivisceral Graft: Donor Procedure

The donor procedure is similar to the liver-intestine procurement. In this case the multivisceral (MV) graft is represented by the liver, stomach, duodenum, pancreas, small bowel, and right and transverse colon (Fig. 24.2). Before donor aortic cannulation, the right colon and the small bowel are fully mobilized from the retroperitoneum, completely exposing the infra-renal vena cava and aorta. After an extended

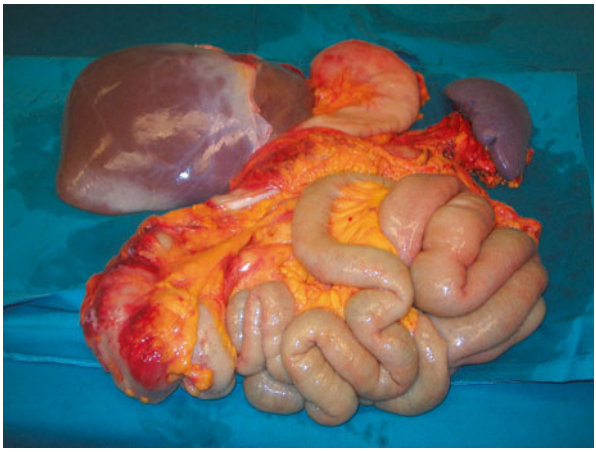

Fig. 24.2 Multivisceral graft represented by the liver, stomach, duodenum, pancreas, small bowel, and right and transverse colon

Kocher maneuver of the duodenum and pancreas, the spleen and distal pancreas are also completely mobilized, and the gastroesophageal junction is cut. Gallbladder flushing is performed. The liver is harvested together with the hepatic vein's cuff superiorly and the inferior vena cava's cuff inferiorly (above the renal veins). All the maneuvers can be performed in an anticlockwise fashion (right colon, small bowel, and transverse colon-spleen and pancreas-esophagus and stomach-duodenum-liver).

Once the entire abdominal viscera have been mobilized and the celiac axis and superior mesenteric artery identified, the infra-renal abdominal aorta is cannulated, then the thoracic aorta is cross-clamped, and perfusion from the aorta of all the abdominal organs can begin.

The harvesting of the multivisceral graft begins with the harvesting of the suprarenal aorta en bloc with the takeoffs of the celiac axis and superior mesenteric artery and finishes with the mobilization of the liver, together with the inferior vena cava as in isolated liver retrieval.

The back-table procedure involves just securing with stitches the lumbar arteries arising from the posterior wall of the suprarenal aorta and ligatures of the lymphatic ducts lying around the celiac axis and superior mesenteric artery.

In the case of a planned modified multivisceral (MMV) transplant (without the liver), the donor liver is separated from the multivisceral gastrointestinal graft by cutting the bile duct and the hepatic artery just distally to the donor gastroduodenal artery. The portal vein is cut as in the case of combined liver and pancreas harvesting for separate transplants. Usually not much length of the portal vein should be left with the multivisceral graft without the liver; any too short portal vein of the MMV graft can be corrected with an iliac vein graft or better with the native portal vein of the MMV graft recipient. The gastroduodenal artery is usually removed with

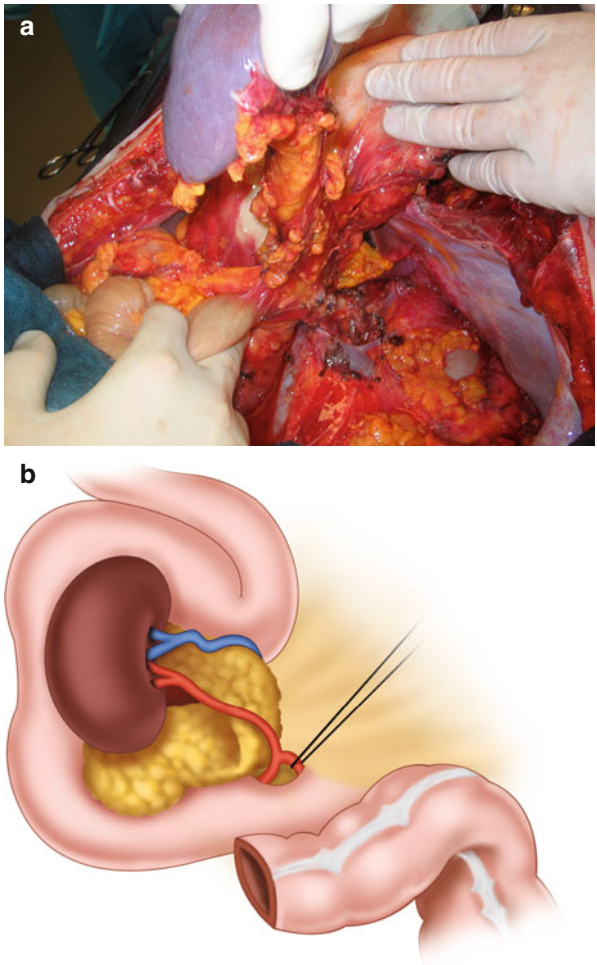

Fig. 24.3 Multivisceral procurement: (**a**, **b**) the pancreas is removed together with the spleen (spleen removed at back-table if necessary) and en bloc with the duodenum

the MV graft, so the hepatic artery must be cut at the proper hepatic artery. The pancreas is removed together with the spleen (the spleen is removed at the back-table if necessary) and en bloc with the duodenum (Fig. 24.3). The stomach is stapled on the esophagus with a TA stapler (Fig. 24.4). Harvesting is concluded by thoracic aortic conduit removal from the donor (to be used as a vascular graft). Pyloromyoplasty can be done at the back-table or during the warm phase. Notably, during the inspection phase, if the left or right branch for the liver is present, the MMV graft must be left: liver transplantation is a life-saving procedure. In this case, always keep an isolated small bowel recipient in-house as a backup, in order to use the graft anyhow.

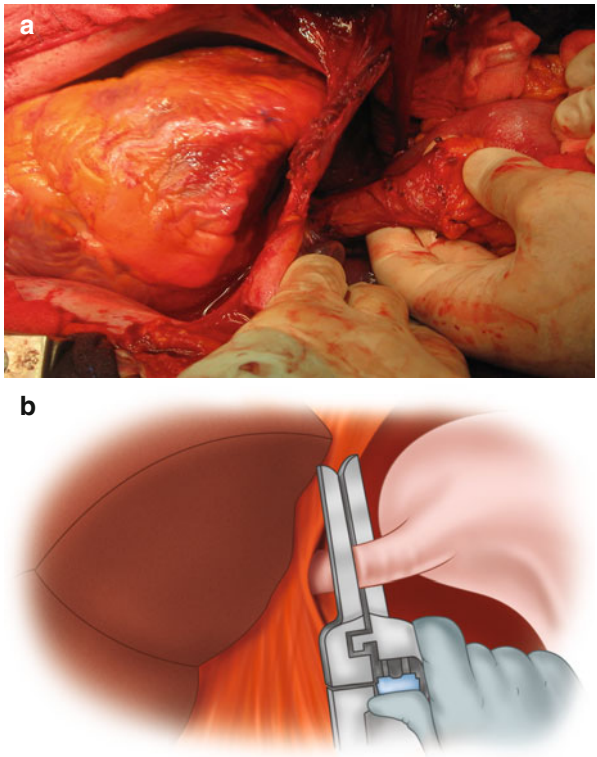

Fig. 24.4 (**a**) Multivisceral procurement: the stomach is stapled on the esophagus with a stapler. (**b**) Schematic representation

References

1. Abu-Elmagd K, Fung J, Bueno J, Martin D, Madariaga JR, Mazariegos G, Bond G, Molmenti E, Corry RJ, Starzl TE, Reyes J. Logistics and technique for procurement of intestinal, pancreatic and hepatic grafts from the same donor. Ann Surg. 2000;232(5):680–87.
2. Zanfi C, Cescon M, Lauro A, Dazzi A, Ercolani G, Grazi GL, Del Gaudio M, Ravaioli M, Cucchetti A, La Barba G, Zanello M, Cipriani R, Pinna AD. Incidence and management of abdominal closure-related complications in adult intestinal transplantation. Transplantation. 2008;85(11):1607–9.
3. Fischer-Frohlich CL, Konigsrainer A, Shaffer R, Schaub F, Pratschke J, Pascher A, Steurer W, Nadaline S. Organ donation: when should we consider intestinal donation. Transpl Int. 2012;25(12):1229–40.
4. Lauro A, Zanfi C, Ercolani G, Dazzi A, Golfieri L, Amaduzzi A, Grazi GL, Vivarelli M, Cescon M, Varotti G, Del Gaudio M, Ravaioli M, Pironi L, Pinna AD. Twenty-five consecutive isolated intestinal transplants in adult patients: a five-clinical experience. Clin Transplant. 2007;21(2):177–85.
5. Greenstein SM, Sun SC, Senitzer D, Schechner RS, Tellis VA. Pretreatment with irradiation and donor-specific transfusion prolongs survival in small intestinal transplantation. Transplant Proc. 1993;25(1pt 1):490–1.
6. Starzl TE, Todo S, Tzakis A, et al. The many faces of multivisceral transplantation. Surg Gynecol Obstet. 1991;172(5):335–44.
7. Nayyar N, Mazariegos G, Ranganathan S, Soltys K, Bond G, Jaffe R, Sun Q, Nucci A, Kosmach B, Squires R, Abu-Elmagd K, Sindhi R. Pediatric small bowel transplantation. Semin Pediatr Surg. 2010;19(1):68–77.

Intestinal/Multivisceral Transplantation 25

Antonio D. Pinna and Chiara Zanfi

25.1 The Embryological Basis of Multivisceral/Small Bowel Transplantation

The grape of the abdominal coelomic organs can be divided from the embryological point of view into three portions: the *foregut* (stomach and duodenum) with the glandular annexes (liver and pancreas), the *midgut* (small bowel and right colon), and the *hindgut* (left colon and rectum). The foregut has an arterial supply provided by the celiac axis; the midgut is vascularized from the superior mesenteric artery (SMA) and the hindgut from the inferior mesenteric artery (IMA). The foregut with the pancreas and the midgut share the same venous outflow through the superior mesenteric vein (SMV) and portal vein, while the hindgut has two venous outflows: the inferior mesenteric vein and the hemorrhoidal venous system. The liver, which is connected to the foregut and midgut by the portal vein and the biliary system, presents a unique double vascular supply which comes from the celiac axis and the portal vein and a single outflow into the inferior vena cava through the hepatic veins.

Transplant of the foregut with the liver has been performed for what was defined as a "cluster transplant" [1], but despite providing some useful information for the development of intestinal transplantation, it will not be discussed here. Transplantation of the hindgut has never been performed due to the complexity of the venous outflow reconstruction and the possible complications secondary to denervation of the rectum. In this chapter we will concentrate primarily on the technical aspects (see also Chap. 24) of transplantation of the midgut (isolated intestinal

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transplant) alone or in combination with the foregut and liver (multivisceral transplantation) or midgut and foregut alone without the liver (modified multivisceral transplantation).

25.2 Nomenclature

Since the initial experience in intestinal transplantation [2], several combinations of the hepato-gastro-enteric systems have been proposed and utilized to treat irreversible failure of the small bowel or small bowel and liver. Recently, Abu-Elmagd et al. [3] published details of three main types of intestinal/multivisceral transplant based on the frequency with which they have been adopted clinically.

Type I is the intestinal transplant which considers the transplant of the small bowel alone or transplantation of the small bowel en bloc with the colon and/or the pancreas.

Type II is the liver-intestine transplant which refers to the transplantation of the liver with the small bowel without the stomach-duodenum and pancreas, where the liver is kept in continuity with the midgut just by the portal vein. This type of graft requires the preservation of the stomach-duodenum and pancreas of the recipient, providing an anastomosis between the native portal vein to the graft portal vein or to the recipient inferior vena cava. Also in this combination, the donor graft can include the right colon.

Type III is the multivisceral graft transplant, which can be *full* when the gastroenteric system together with the liver and pancreas is transplanted en bloc or *modified* when the stomach-duodenum-pancreas and intestine are transplanted en bloc without the donor liver. In particular cases this modified multivisceral transplant has been performed maintaining also the native pancreaticoduodenal complex and the spleen (Fig. 25.1).

25.3 Graft Types and Indications

The use of the three main types of intestinal graft has changed over time, depending on the experience of the surgical team and the change in indications for intestinal transplantation. A paper published in 2009 examined the shifting of graft types over time in a large cohort (500 patients) of intestinal transplants performed over an 18-year period [4]. Dividing the 18-year experience in intestinal/multivisceral transplantation into three eras, Era I (1990–1994), Era II (1995–2001), and Era III (2001–2008), the indications rose from 35 % in Era I to 46 % in Era III for isolated intestinal transplants and from 20 % in Era I to 34 % in Era III for multivisceral transplantation. On the contrary, liver-intestinal transplants (type II) decreased from 45 % (Era I) to 20 % (Era III) with prevalent indications in pediatric patients. The polarization of the intestinal grafts in isolated intestine and multivisceral transplant reflects an almost international attitude and is due to early referrals of irreversible intestinal failure patients to transplant centers (isolated intestinal transplants) and the technical complexity of the liver-intestinal transplant compared to multivisceral transplantation.

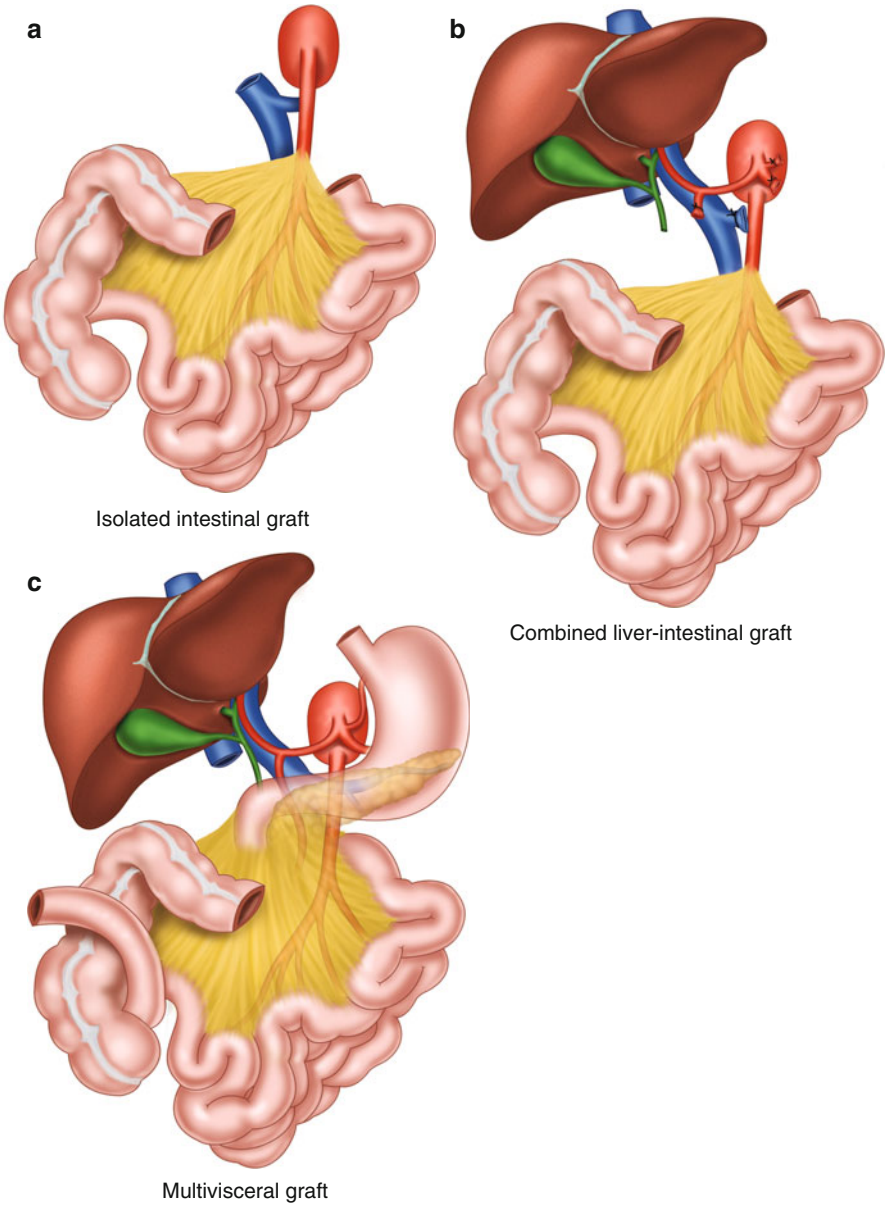

Fig. 25.1 Graft types: (**a**) isolated intestinal graft; (**b**) combined liver-intestinal graft; (**c**) multivisceral graft

25.4 Isolated Small Bowel Transplantation

The main indication for the transplant of the isolated midgut is any intestinal irreversible failure with normal liver function and no necessity to replace the stomach and the duodenum secondary to anatomical damage or dysmotility of these two organs. A variety of diseases can be treated with this transplant in adults and children: congenital

or acquired anatomical shortening of the small bowel, diffuse dysmotility or congenital intestinal villi dysfunction, and desmoid tumors (see also Chap. 24). The small bowel can be transplanted alone or in continuity with the right colon to provide better absorption; in a few patients, the intestinal graft was transplanted with preservation of the enteric nervous ganglia, but no data exist on the outcome of ganglia preservation. The isolated intestinal graft can be transplanted reducing its size in the case of a small residual abdominal cavity, and of course it can be a perfect type of graft if there is an indication for living related transplantation, particularly from adult to child.

25.4.1 Recipient Procedure

After careful laparotomy, a total enterectomy of the recipient's residual small bowel is performed, if needed. The small bowel graft with or without the right colon can be revascularized orthotopically or heterotopically. In the first case, the SMA is anastomosed end-to-end to the recipient's SMA with 7-0 Prolene, and the same is done with the SMV of the donor and recipient. In the case of previous recipient SMA disease, the arterial inflow should be obtained with an interposition arterial graft from the recipient aorta and then with an anastomosis between the donor SMA and the arterial graft (Fig. 25.2). An orthotopical variant of the venous outflow is to anastomose the donor superior mesenteric vein end-to-side to the recipient portal

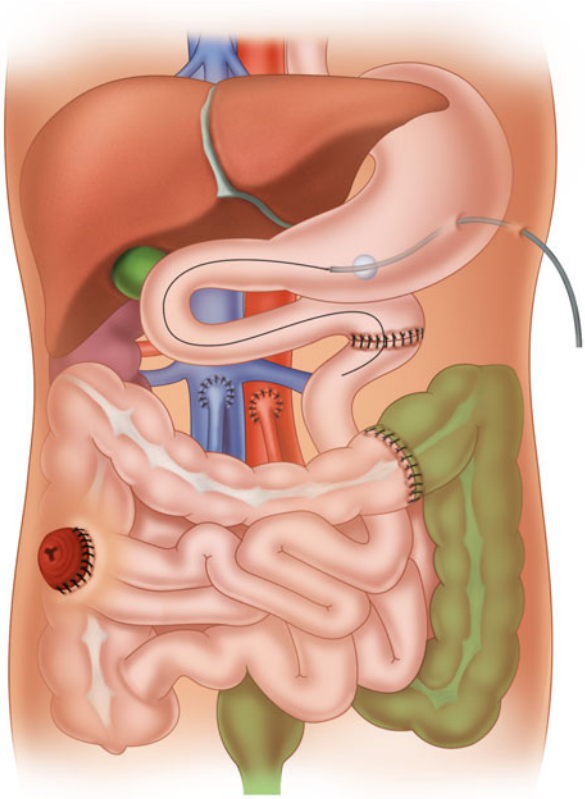

Fig. 25.2 Isolated intestine transplant (From Bozzetti et al. [18], with permission)

vein. This procedure is sometimes more difficult than the others and requires an extended mobilization of the recipient's pancreas and duodenum and exposure of the portal vein without damaging the recipient bile duct [5].

In the case of difficult dissection of the superior mesenteric vein or previous thrombosis of the recipient SMV and if the surgeon does not want to perform an orthotopic SMV reconstruction with the portal vein as described previously, a heterotopic revascularization of the intestinal graft can be performed (Fig. 25.3). In this case, after the enterectomy of the residual intestine, the surgeon should expose the anterior and lateral walls of the infrarenal aorta and inferior vena cava. After partial clamping of the aorta and IVC, an arterial graft and a venous graft from the donor are anastomosed end-to-side to the recipient's large abdominal vessels. Finally, first the donor SMA is anastomosed to the arterial graft followed by the anastomosis between the donor SMV and the vein graft. It should be emphasized that the heterotopical revascularization of the intestinal allograft facilitates its implantation. However, special attention should be paid to avoid kinking of the artery and vein by excessive length of the two vessels.

At the time of the initial clinical experience in small bowel transplantation, there was concern about possible native liver dysfunction in using this heterotopical venous reconstruction. Later, it was observed that reconstruction of the donor superior mesenteric vein into the systemic circulation did not cause any liver dysfunction and could be considered as effective as direct reconstruction into the portal venous system [6].

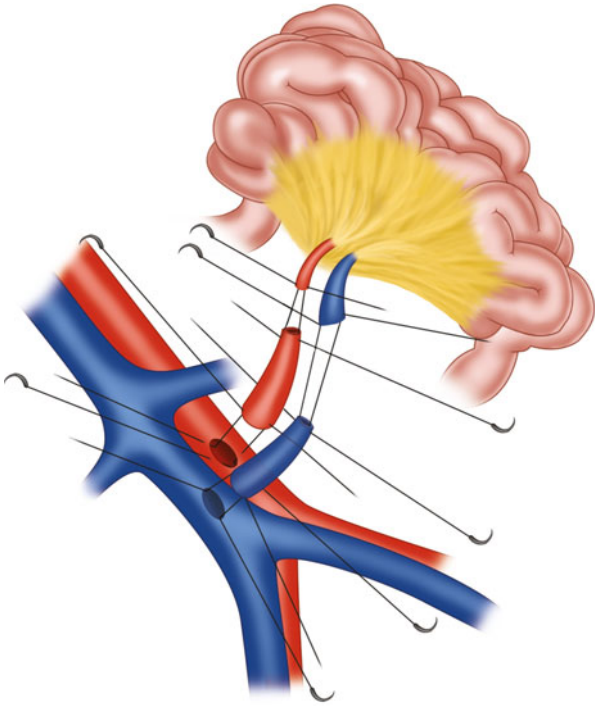

Fig. 25.3 Eterotopic revascularization of the intestinal graft

Tzakis et al. [7] first described the inclusion of the right colon in the isolated small bowel transplant graft. The supposed advantage of including the right colon was to improve the electrolytes and water absorption by the graft. Initial concerns were the possible increase in rejection of the colon segment and the subsequent increase in mortality rates of the recipients. In the first review of the results of such composite grafts done by the *International Intestinal Transplant Registry* in 2007, patients transplanted with isolated intestine together with the colon showed a significantly lower requirement of i.v. fluids or parenteral nutrition early and later after transplantation. Furthermore, no significant differences were reported in terms of mortality or rejection when intestine plus colon was compared to small bowel graft alone.

Once the graft has been revascularized and hemostasis obtained, the intestinal continuity is reconstructed proximally with the fourth portion of the duodenum or the stomach of the recipient. Distally the small bowel or the right colon is reconstructed with the remaining left colon or sigmoid colon. In some conditions, an endorectal pull-through with sphincter preservation and rectal mucosectomy is indicated. This quite difficult procedure can be indicated in cases of multiple juvenile polyposis extended into the rectum or in the case of Hirschsprung's disease with diffuse dysmotility extended from the rectum to the jejunum [7]. After bowel reconstruction, the surgery ends with the feature of the terminal ileostomy, having first placed an enteric feeding tube into the intestinal allograft. The distal stoma is necessary in order to obtain easy access to the intestinal allograft for intestinal biopsy and endoscopy. Some centers also advocate creating a proximal stoma to improve the immunological monitoring of the graft also for enteral nutrition. Of course, depending on personal choices, it is better to remember that stomas need to be closed at some time, and stoma closure is not without complications in such patients. The distal stoma is without question an extreme need for immunological monitoring; for differential diagnosis during the follow-up endoscopies, it is important to observe the bowel mucosa and perform biopsies of the allograft intestine and of the native bowel. Nutrition of the allograft can be obtained placing a transgastrostomy feeding tube long enough to reach the lumen of the allograft intestine.

25.5 Combined Liver-Intestine Transplantation

This composite graft, together with isolated intestinal transplantation, was one of the first models of intestinal transplant performed. The principal indications consist of irreversible intestinal failure combined with cholestatic cirrhosis with portal hypertension. The main patient population which may require this type of allograft is pediatric. The combination of a liver-intestine allograft invariably requires the sparing of the native stomach-pancreas and duodenum with preservation of their vascular supply through the native celiac axis and superior mesenteric artery and providing the venous outflow through a portacaval shunt to be performed before vascular anastomosis of the composite graft. Due to the fact that this type of allograft was used more often in children, several kinds of reduced size grafts have been performed.

25.5.1 Recipient Procedure

After removal of the residual small bowel and colon, the total native hepatectomy is performed with the piggyback technique. After the dissection of the native bile duct, the hepatic artery is cut distal to the gastroduodenal artery. The portal vein is clamped and cut up into the hilum. At this point, with the liver devascularized, the native proximal portal vein is anastomosed to the native inferior vena cava in end-to-side fashion with running sutures and unclamped to avoid congestion of the native gastro-pancreatic-duodenal bloc. After complete mobilization of the native liver, hepatectomy is performed after clamping of the hepatic vein confluence.

The liver-intestine allograft is then placed on the surgical field, and the first arterial reconstruction is performed. This can be done anastomosing the donor aortic patch on the anterior wall of the recipient's infrarenal aorta or, more easily, anastomosing first a segment of the donor's thoracic aorta end-to-side to the anterior wall of the infra-renal recipient aorta, followed by the anastomosis of the aortic carrel patch including the takeoff of the donor celiac axis and SMA to the aorta conduit in end-to-end fashion with running sutures. There are two main pitfalls in this kind of arterial reconstruction: (a) if the aortic patch around the donor SMA is too short, the inferior wall of the aorta conduit may partially close the takeoff of the SMA; (b) if the aortic conduit is too long, this can kink, producing a critical arterial flow to the SMA or both SMA and celiac axis.

After completion of the arterial reconstruction, the liver is put in place in the right sub-diaphragmatic space, and the venous outflow is reconstructed, anastomosing the donor inferior caval vein to the confluence of the recipient's hepatic veins. Only at this point is the liver-intestine allograft reperfused through the arterial reconstruction. Once complete hemostasis has been obtained, the intestinal continuity is performed, anastomosing first the proximal donor jejunal loop to the donor bile duct, followed by the anastomosis between the native fourth portion of the duodenum to the allograft jejunum and, finally, by the anastomosis between the native colon and the allograft last ileal loop just proximally to the segment of donor ileum which can be exteriorized for the temporary ileostomy (Fig. 25.4). A jejunal feeding tube is placed through a gastrostomy and pushed into the allograft jejunum through the duodenal-jejunal anastomosis.

25.5.2 Pitfalls of the Liver-Intestine Transplant Technique

Besides the arterial pitfalls described before which are rare but possible, there are two other major pitfalls in this procedure which we should be aware of. The first and the most frequent is the biliary tract reconstruction. Biliary complications secondary to the biliary-jejunal anastomosis are similar in rate to what one should expect after roux-en-Y biliary reconstruction in pediatric liver transplantation. The major concern is that in over-immunosuppressed patients, like intestinal transplant patients, this can become a life-threatening complication if not diagnosed promptly.

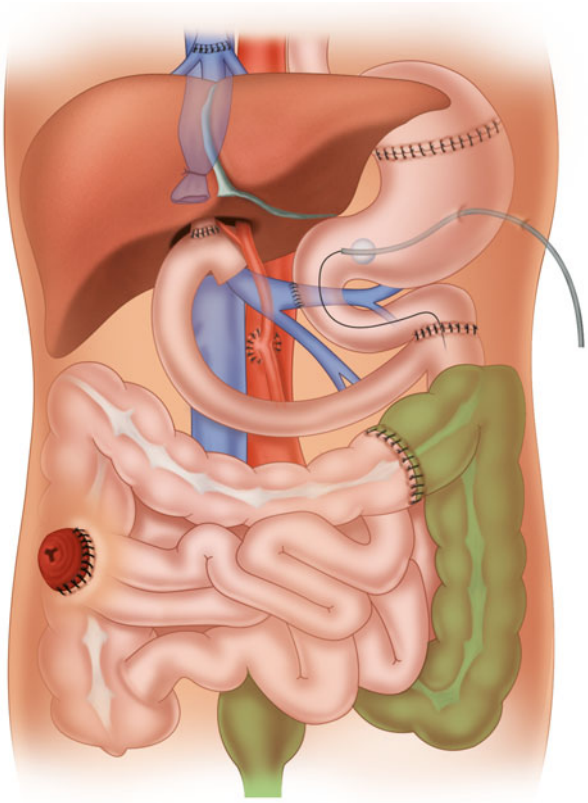

Fig. 25.4 Combined liver-intestine transplantation (From Bozzetti et al. [18], with permission)

The second pitfall is due to the absence of supporting tissue around the donor's portal vein/superior mesenteric vein conduit which, after total pancreatectomy, can become too long and prone to kinking and portal vein thrombosis.

In order to avoid these two possible complications, such as biliary stricture/leakage or portal vein kinking, several modifications to the original technique as described previously have been proposed.

Initially, the group from Omaha proposed performing (at the back table) a subtotal donor pancreatectomy, leaving the donor duodenum and the head of the pancreas in continuity with the donor bile duct, thereby avoiding biliary reconstruction and leaving some pancreatic tissue anterior to the donor portal vein. Although it is true that this method avoided two possible complications, a different one was described following this modification: a pancreatic fistula from the suture of the pancreatic remnant. The natural evolution of the in any case brilliant idea of the Omaha group was the one proposed later by the Miami group, which considered transplanting the entire donor pancreas and duodenum in continuity with the donor liver and small bowel. With this latest evolution of the liver-intestine allograft transplantation, the recipient will end the transplant with two pancreata, no biliary anastomosis, and less chance of portal vein kinking. No evidence of dangerous hypoglycemic episodes had been reported with the presence of two functioning pancreata.

25.5.3 Allograft Size Reduction

The presence of size discrepancies between donor and recipient may sometimes require graft size reduction in order to accomplish the full or partial closure of the abdominal cavity. The allograft size reduction can be obtained by reducing the liver, the small bowel, or both.

The liver reduction can be obtained with resection of the left lobe, transplanting the right trisegmental liver allograft or transplanting the left lateral segment after considerable reduction of the liver allograft [8].

The small bowel can be reduced by resecting the mid jejunum, avoiding deleterious functional loss of the transplanted bowel. The two graft reductions can be combined in the case of large size discrepancies.

Abdominal wall transplantation has been described to solve this frequent problem of size (see Chaps. 26 and 27).

25.6 Multivisceral Transplantation

Multivisceral abdominal transplantation with the liver was first described in dogs by Starzl in 1960 [9]. It was the first type of intestinal transplant performed clinically, and centers performing multivisceral transplantation nowadays substantially adopt the same surgical technique as then [10]. There are several indications for performing a multivisceral transplantation, schematically: any kind of irreversible intestinal failure which causes irreversible liver failure and where the need to remove the stomach and the pancreas is due either to extension of the disease to these upper abdominal organs or because of vascular damage to the celiac axis and/or the superior mesenteric artery. *Short bowel syndrome with liver failure* and complete *splanchnic venous thrombosis* are the main stems of the various diseases that can be treated with a multivisceral transplantation. *Gardner's syndrome with desmoid tumors* in the mesenteric root infiltrating the visceral arteries is another well-accepted indication for multivisceral transplantation. There are also several hollow visceral myopathies or neuropathies that can benefit from a multivisceral transplant sparing the native liver (see also Chap. 24).

25.6.1 Recipient Procedure

25.6.1.1 Full Multivisceral Graft

The surgical procedure in candidate recipients for a full multivisceral graft (with the liver) is quite simple, requiring the resection of all the remaining bowel, a total gastrectomy combined with total pancreatectomy, and a total hepatectomy with piggyback technique. Despite the easy principles of the pre-implant phase of the procedure, the surgery can sometimes be severely complicated by the presence of portal vein collaterals with bleeding from portal hypertension in patients who have often undergone previous multiple surgery and have dense vascularized adhesions. In order to decrease the risk of large amounts of blood loss, several strategies have

been adopted. One possibility is to perform a transfemoral arterial embolization of the celiac axis and superior mesenteric artery once the donor surgeon has given assurance of the organs' quality. Another way is to start, after laparotomy, with dissection of the recipient's gastroesophageal junction. After the stomach has been mobilized from the esophagus and the left lobe of the liver mobilized and rotated to the right, the retro-gastric space is open, and the surgeon can attempt to clamp the celiac axis from above. The successful dearterialization of the stomach, pancreas, spleen, and liver can permit a relatively bloodless mobilization of the spleen and pancreas so as to obtain a left access to the proximal trunk of the superior mesenteric artery which can then also be clamped. Once control of the main arteries has been achieved, the final dissection of the stomach, pancreas, and remaining small bowel can be easily performed, leaving the proximal trunk of the celiac axis and superior mesenteric artery clamped. At this point, the hepatectomy with piggyback technique can be completed, leaving a clamp on the hepatic vein confluence.

25.6.1.2 Modified Multivisceral Graft

In patients where the liver is not required, the important step of the demolition part of the procedure is the isolation and sparing of the entire hepatic artery. Once the bile duct has been cut, the proper hepatic artery is visualized and followed proximally. The right gastric artery, the gastroduodenal artery, and all the pancreatic arterial branches arising from the hepatic artery are cut between ligatures. The hepatic artery is followed as far as its origin from the celiac axis. After the left gastric artery has been cut between ligatures, the splenic artery is carefully dissected just at its emergence from the celiac axis and cut between ligatures. The ligature on the proximal stump of the splenic artery is reinforced with a stitch. At this point, the stomach is cut at the level of the cardias. The spleen and distal pancreas are mobilized from left to right, and a Kocher maneuver of the duodenum and head of the pancreas is performed. The proximal trunk of the superior mesenteric artery is visualized and is clamped and cut. With the entire gastro-pancreatic-intestinal bloc in the surgeon's hands, the portal vein is clamped distally toward the liver and cut as low toward the superior mesenteric vein as possible, obtaining a good length of portal vein which can be useful if the donor portal vein should be too short.

25.6.1.3 Vascular Reconstruction (Full Multivisceral and Modified Multivisceral Graft)

Once perfect hemostasis has been obtained, the arterial reconstruction of the multivisceral graft must be done first. Several kinds of arterial reconstructions have been described, all of them suggesting, in one way or another, the need to keep the takeoff of the celiac axis and superior mesenteric artery together and the use of the donor aorta. The infrarenal donor abdominal aorta can be anastomosed directly to the recipient infrarenal or supraceliac aorta end-to-side. The same kind of aortic-aortic anastomosis can be performed using first a segment of the donor thoracic aorta as an aortic conduit. The open end of the donor abdominal aorta with the celiac axis and superior mesenteric artery can be closed with a patch of donor aorta to avoid slipping of the ligature or, even worse, dissection of the aortic intima [11]. Girlanda

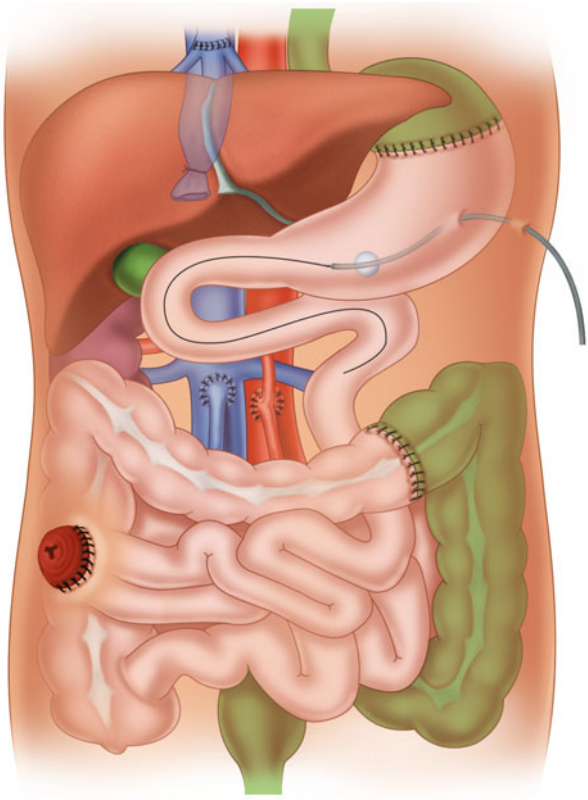

Fig. 25.5 Multivisceral transplantation (From Bozzetti et al. [18], with permission)

et al. [12] have also described other methods of rearterialization of a multivisceral graft in the case of multiple visceral arterial anomalies [12].

The venous outflow is usually performed anastomosing the suprahepatic donor inferior vena cava to the confluence of the recipient's hepatic veins (Fig. 25.5). Sometimes, the donor suprahepatic cava is anastomosed in piggyback to the recipient retrohepatic inferior vena cava if there is discrepancy between the donor inferior caval vein and the recipient hepatic vein confluence.

The only difference in the vascular reconstruction of the *modified multivisceral graft* lies in the reconstruction of the venous outflow of the graft which is done by anastomosing the two portal veins end-to-end (Fig. 25.6). In a large cohort of 100 consecutive multivisceral transplants performed at the University of Miami, the arterial reconstruction was principally performed with an anastomosis to the recipient infrarenal aorta with an interposed aortic conduit. The venous outflow was always with a portal-vein-to-portal-vein anastomosis in patients receiving a *modified multivisceral graft*. In more than two-thirds of recipients receiving a *full multivisceral graft*, the venous outflow was obtained with an anastomosis between the donor suprahepatic vena cava to the hepatic vein confluence of the recipient [13].

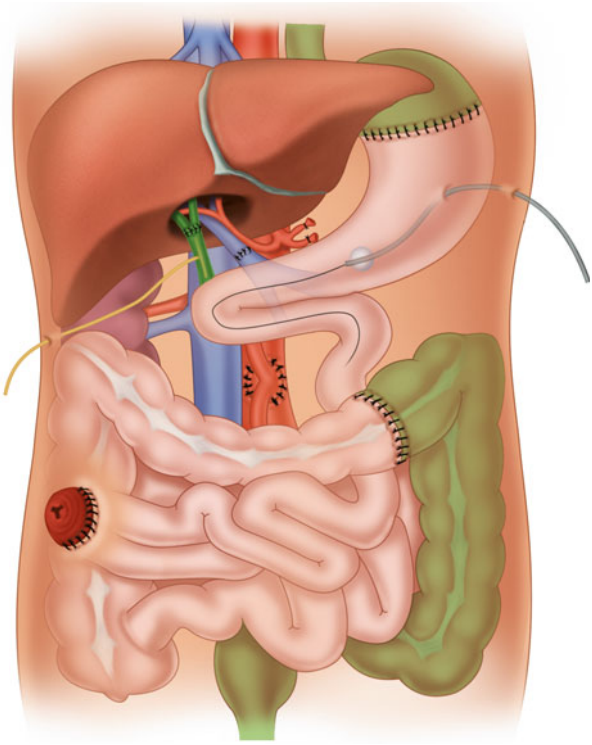

Fig. 25.6 Modified multivisceral transplantation (From Bozzetti et al. [18], with permission)

25.6.1.4 Intestinal Reconstruction

Gastrointestinal continuity is achieved by performing first an esophagogastric anastomosis and completed with the anastomosis between the donor intestine and the native colon just proximally to the end ileostomy. In the case of a *modified multivisceral* transplantation, a biliary reconstruction is required. This is usually achieved with a duct-to-duct biliary anastomosis over a T-tube. Because of the inevitable intestinal organ denervation, a pyloroplasty is performed for gastric drainage.

25.6.1.5 Technical Variants

Some further modifications of the *modified multivisceral transplant* have been proposed for different reasons. In 2007, Matsumoto proposed performing a multivisceral transplant sparing not only the liver but also the native pancreas and spleen in the recipient [14]. Others proposed the same type of multivisceral transplant, preserving only the native spleen but with a total pancreaticoduodenectomy of the recipient [15]. According to the authors who proposed the preservation of the native spleen and pancreas, the advantages of this procedure are the decreased risk of infection and/or posttransplant lymphoproliferative disease. The preservation of the native

pancreas and the presence at the end of the transplant of two functioning pancreata can increase the islet cell mass, thus reducing the risk of posttransplant diabetes.

25.7 Special Issues in Intestinal/MV Transplantation

25.7.1 To Spleen or Not to Spleen

Recently several centers have suggested including the donor spleen in the case of *liver-intestine* type or *multivisceral type* transplantation. Technically speaking, there are no particular issues except for the fact that extreme care should be taken to avoid tearing the splenic capsule and rotation of the spleen around the axis of the splenic artery and vein. The primary objective of including the spleen in such types of intestinal transplants is to improve the recipient's defense against infections by avoiding the asplenic state; a secondary aim is the possibility of reducing rejection by increasing the mass of immunocompetent cells of donor origin according to the expansion-deleting leukocytes theory for tolerance induction in solid organ transplantation. However, despite a few reported cases and some spleens having to be taken out secondary to surgical complications, some patients who underwent intestinal transplantation with the donor spleen developed severe immune hemolysis.

In a series published by the Miami group in 2009, the authors concluded that including the spleen in multivisceral transplantation can be performed without significantly increasing the risk of graft-versus-host-disease [16]. However, the allogeneic spleen seems to have a modest protective effect on small bowel rejection, and autoimmune hemolysis is a concern, and this issue definitely requires further investigation.

25.7.2 The Kidney

Renal failure is one of the most frequent long-term complications after intestinal transplantation. High levels of immunosuppression for a longer time need antifungal therapy, and dehydration from enteric losses before and after transplant, in the case of graft dysfunction, is the main reason why a higher rate of patients develops chronic renal failure after small bowel transplantation. This complication becomes almost inevitable in patients who undergo retransplantation of the small bowel. For this small group of patients, associating a kidney transplant at the same time as the intestinal transplantation has been advocated. The kidney graft can be classically transplanted eterotopically in the right lower abdominal quadrant or alternatively, in the case of multivisceral transplantation, en bloc with the multivisceral graft, keeping the renal artery in continuity with the abdominal aorta and the visceral vessels. The renal vein in this case can be reconstructed end-to-side to the inferior caval vein of the recipient before the outflow reconstruction of the multivisceral graft. The reconstruction of the donor's ureter will be done with the usual technique, attaching it to the recipient's bladder or alternatively, if too short, to the recipient's ureter [17].

References

1. Alessiani M, Tzakis A, Todo S, Demetris AJ, Fung JJ, Starzl TE. Assessment of five-year experience with abdominal organ cluster transplantation. J Am Coll Surg. 1995;180(1):1–9.
2. Starzl TE, Todo S, Tzakis A, Alessiani M, Casavilla A, Abu-ElMagd K, Fung JJ. The many faces of multivisceral transplantation. Surg Gynecol Ostet. 1991;172(5):335–44.
3. Abu-Elmagd K. The small bowel contained allografts: existing and proposed nomenclature. Am J Transplant. 2011;11(1):184–5.
4. Abu-Elmagd KM, Costa G, Bond GJ, Soltys K, Sindhi R, Wu T, Koritsky DA, Schuster B, Martin L, Cruz RJ, Murase N, Zeevi A, Irish W, Ayyash MO, Matarese L, Humar A, Mazariegos G. Five hundred intestinal and multivisceral transplantations at a single center: major advances with new challenges. Ann Surg. 2009;250(4):567–81.
5. Tzakis AG, Todo S, Reyes J, Nour B, Fung JJ, Starzl TE. Piggyback orthotopic intestinal transplantation. Surg Gynecol Ostet. 1993;176(3):297–8.
6. Berney T, Kato T, Nishida S, Tector AJ, Mittal NK, Madariaga J, Nery JR, Cantwell GP, Ruiz P, Tzakis AG. Portal versus systemic drainage of small bowel allografts: comparative assessment of survival, function, rejection, and bacterial translocation. J Am Coll Surg. 2002;195(6):804–13.
7. Tzakis AG, Nour B, Reyes J, Abu-Elmagd K, Furukawa H, Todo S, Starzl TE. Endorectal pull-through of transplanted colon as part of intestinal transplantation. Surgery. 1995;117(4):451–3.
8. Reyes J, Mazariegos GV, Bond GM, Green M, Dvorchik I, Kosmach-Park B, Abu-Elmagd K. Pediatric intestinal transplantation: historical notes, principles and controversies. Pediatr Transplant. 2002;6(3):193–207.
9. Starzl T, Kauup Jr HA. Mass homotransplantations of abdominal organs in dogs. Surg Forum. 1960;11:28–30.
10. Starzl TE, Rowe MI, Todo S, Jaffe R, Tzakis A, Hoffman AL, Esquivel C, Porter KA, Venkataramanan R, Makowka L, et al. Transplantation of multiple abdominal viscera. JAMA. 1989;261(10):1449–57.
11. Nishida S, Vaidya A, Kato T, Nakamura N, Madariaga J, Tzakis A. Use of donor aorta for arterial reconstruction in paediatric liver and multivisceral transplantation. Br J Surg. 2004;91(6):705–8.
12. Girlanda R, Desai CS, Matsumoto CS, Kaufman SS, Little CA, Fishbein TM. Complex arterial reconstruction in multivisceral transplantation. Am J Transplant. 2010;10(3):698–701.
13. Tzakis AG, Kato T, Levi DM, Defaria W, Selvaggi G, Weppler D, Nishida S, Moon J, Madariaga JR, David AI, Gaynor JJ, Thompson J, Hernandez E, Martinez E, Cantwell GP, Augenstein JS, Gyamfi A, Pretto EA, Dowdy L, Tryphonopoulos P, Ruiz P. 100 multivisceral transplants at a single center. Ann Surg. 2005;242(4):480–90.
14. Matsumoto CS, Fishbein TM. Modified multivisceral transplantation with splenopancreatic preservation. Transplantation. 2007;83(2):234–6.
15. Cruz Jr RJ, Costa G, Bond GJ, Soltys K, Rubin E, Humar A, Abu-Elmagd KM. Modified multivisceral transplantation with spleen-preserving pancreaticoduodenectomy for patients with familial adenomatous polyposis Gardner's Syndrome. Transplantation. 2011;91(12):1417–23.
16. Selvaggi G, Nishida S, Levi D, Moon J, Island E, Tekin A, Weppler D, Tzakis A. Intestinal and multivisceral transplantation at the University of Miami. Clin Transpl. 2009; 211–7.
17. Kato T, Ruiz P, Thompson JF, et al. Intestinal and multivisceral transplantation. World J Surg. 2002;26:226.
18. Bozzetti F, Staun M, Van Gossum A, editors. Home parenteral nutrition. Wallingford: CAB International; 2006.

Abdominal Wall Transplantation and Technique

26

Riccardo Cipriani, Luca Negosanti, Valentina Pinto, Rossella Sgarzani, Chiara Gelati, and Federico Contedini

26.1 Introduction

Many patients undergoing intestinal or multivisceral transplantation may encounter severe abdominal wall closure problems at the end of transplantation, resulting in increased morbidity and mortality. Properly cover transplanted organs is mandatory to reduce postoperative complications.

The candidates for intestinal, or multivisceral transplantation, may have a past history of complete midgut removal with the loss of the domain of the abdominal compartment or have severely damaged abdominal walls from repeated laparotomies or enterocutaneous fistulae (Fig. 26.1). The closure of the abdominal wall after intestinal transplantation may represent a significant problem, particularly in patients with previous abdominal surgery, because of the restricted volume of the recipient abdominal cavity, the donor–recipient size discrepancy, and the occurrence of intraoperative edema of the intestinal loops (Fig. 26.2) [1].

The main problems that may lead to a difficult abdominal closure are [2, 3]:

- Multiple previous laparotomies
- Enterocutaneous fistulae
- Donor to recipient unfavourable weight ratio
- Postoperative edema
- Presence of scar and fibrosis from previous surgery

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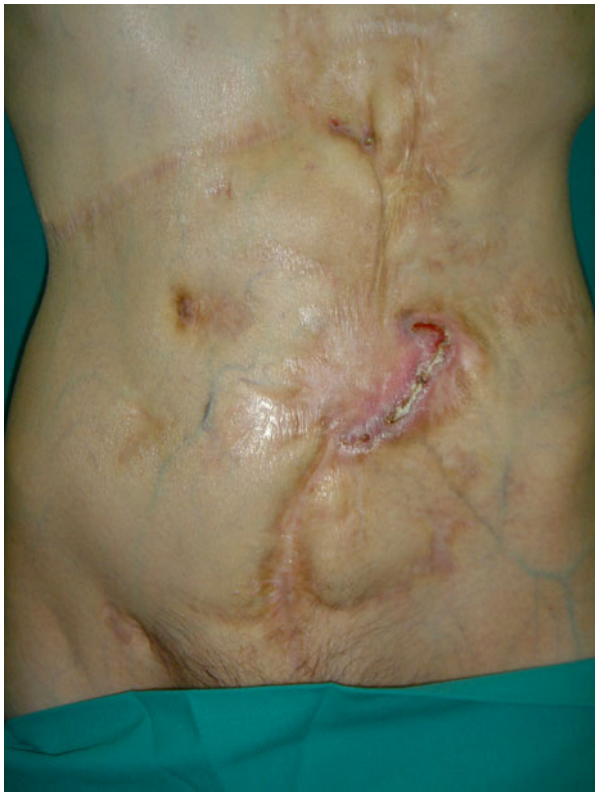

Fig. 26.1 Patient candidate for abdominal wall transplantation. The wall is severely damaged from repeated laparotomies and enterocutaneous fistulae

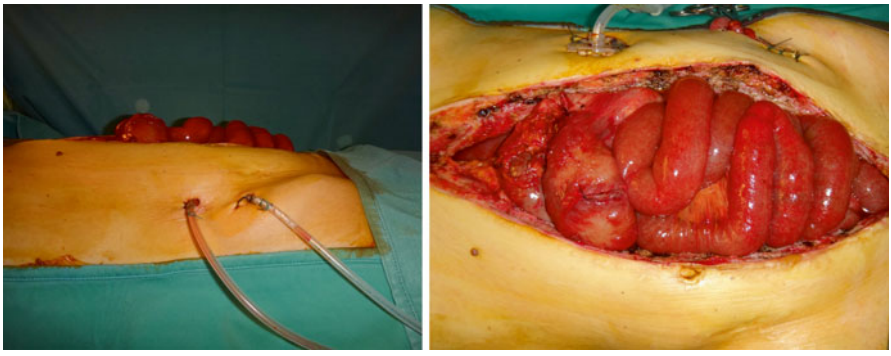

Fig. 26.2 At the end of bowel transplantation, the recipient abdominal wall is not able to properly cover the graft

Furthermore, in this kind of transplantation, diversion stomata and intraperitoneal drains are required, leading to a challenging abdominal wall closure.

Abdominal closure under tension might result in a wide range of complications, such as wound dehiscence, infections, necrosis, exposure of bowel loops, vascular thrombosis of the graft, abdominal compartment syndrome, and respiratory complications [4].

For all these reasons, abdominal wall transplantation was proposed for closure of patients undergoing both intestinal and multivisceral transplantation. The use of a composite tissue allograft in such patients has the main advantage of solving a big problem without requiring further immunosuppression. Abdominal wall transplantation is a feasible and safe procedure: it allows primary closure of the abdomen, avoids the potential morbidity of exposed viscera, and permits early mobilization and rehabilitation of these patients. The technique was first described by Levi et al. in 2003 [5], and, nowadays, whenever possible, it is the first choice to overcome a difficult closure.

The procurement of the abdominal wall graft does not interfere with the procurement of other organs and tissues. Transplantation of the abdominal wall composite graft can take place during the intestinal transplant procedure or several days later with a graft from a different donor. Delaying implantation of the abdominal wall graft allows perioperative edema to diminish before abdominal closure and the patient's condition to stabilize. This strategy may be preferable when the recipient has a particularly large defect in the abdominal wall: in these cases a temporary negative pressure therapy is applied to reduce the infection risk.

In 2006 [6], our group described the first cases of abdominal wall transplantation performed with microsurgical technique, comparing our approach and Levi's one. Nowadays, the microsurgical approach is well defined, and the technique is standardized.

26.2 Surgical Technique

The abdominal wall composite graft described by Levi is a full-thickness, vascularized, myocutaneous free flap. In the original description, it consists of one or both rectus abdominis muscles, with the investing fascia, the overlying subcutaneous tissue, and the skin, and the blood supply is derived from the donor inferior epigastric vessels, left in continuity with the larger iliac vessels. Procurement of the graft was done as part of the cadaveric, heart-beating donor, multiorgan procurement procedure [7, 8]. The procedure began with a bisubcostal incision. Longitudinal incisions were made following both lateral edges of the rectus muscles. These incisions were continued into the groins bilaterally. The common iliac vessels were identified. Finally, a transverse, suprapubic incision was made, connecting the two longitudinal incisions. The abdominal wall graft was packed with ice in situ during other organs procurement; then the distal aorta was cannulated, and the graft was flushed with cold preservation solution. The graft was removed in one piece with the iliac vessels, with a short segment of distal aorta and inferior vena cava. Closure of the donor's abdomen was facilitated by mobilizing skin and subcutaneous tissue flaps from the lateral abdomen and flanks.

The abdominal wall graft is transplanted as a separate organ. The inclusion of an abdominal wall graft added about 2 h to the procedure's operative time. The vessels of the abdominal wall graft were implanted into the recipient's common iliac artery and vein. Alternatively, the infrarenal aorta and inferior vena cava can be used as recipient vessels.

The graft was sutured in layers to the recipient's abdominal wall during closure of the abdomen. The graft, with its long vascular pedicle, was rotated and positioned according to location of the abdominal wall defect. The skin of the abdominal wall graft was left intact; normal skin color indicated adequate perfusion. The flow through the inferior epigastric vessels of the graft was monitored with a handheld Doppler ultrasound device. Biopsies of the skin of the graft were undertaken randomly and when rejection was suspected on clinical grounds.

26.3 Microsurgical Technique

The microsurgical approach was introduced in S.Orsola-Malpighi Hospital in Bologna in 2006 [6]. Abdominal wall harvest is part of a multiorgan procurement. The flap consists in a median oval cutaneous isle extended from xiphoid to pubis and from one oblique muscle to the other; the flap is composed of cutaneous and subcutaneous tissues, both rectus abdominis muscles and a small part of the oblique ones, the deep muscular sheet, and parietal peritoneum (Fig. 26.3). The vascular

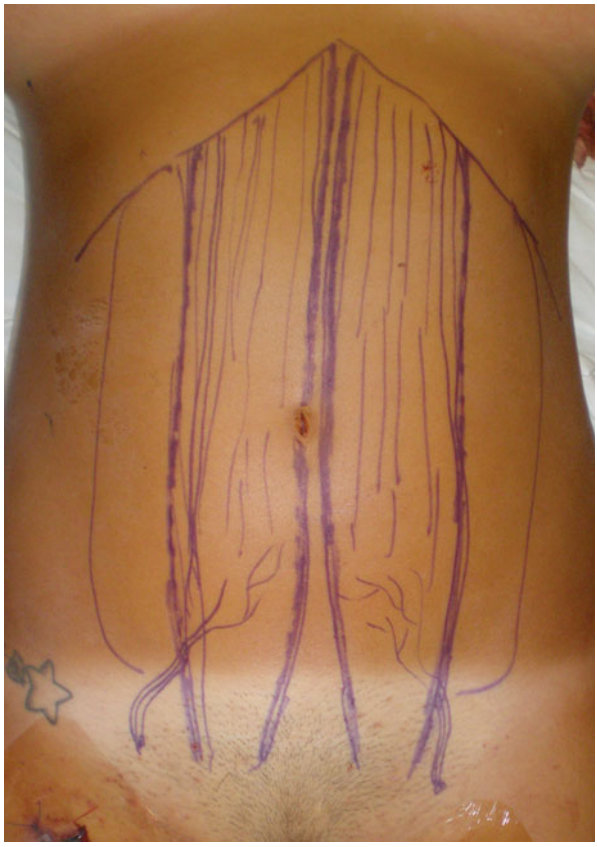

Fig. 26.3 Preoperative drawing on donor abdominal wall

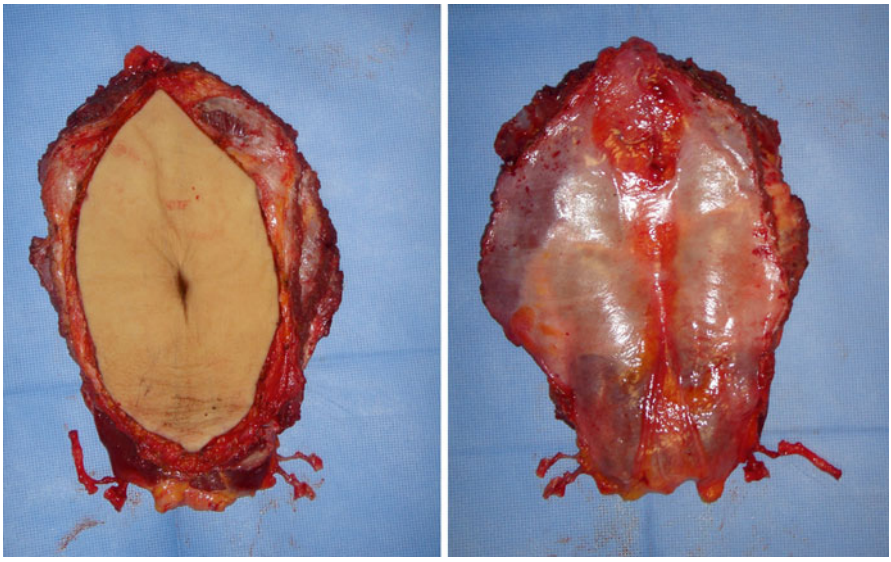

Fig. 26.4 Abdominal wall flap at the end of harvesting from donor

pedicle consisted in the deep inferior epigastric arteries and veins, isolated bilaterally, if possible. The flap is designed and harvested by a microsurgeon. Flap harvesting starts with a superior incision made until trough skin and subcutaneous tissues including the deep fascia under rectus muscles; then the flap is dissected preserving laterally a small part of oblique muscles. The dissection is stopped at the inferior edge of the flap, and the abdominal flap is turned over to face downwards to allow the procurement of the other abdominal organs. During this phase, the flap is packed with cold water and ice, while the other organs are flushed with preservation solution during their harvesting. After that, the pedicles of the abdominal wall flap are sectioned at the origin from iliac vessels (Fig. 26.4). A further cold perfusion is performed through incannulation of the two epigastric arteries; the abdominal graft is then stored in a conservation container with ice. Donor site is repaired by direct closure, after generous undermining of the residual lateral abdomen and flanks tissues.

The abdominal wall transplantation is performed after abdominal organs transplantation. The donor epigastric pedicles are anastomosed end-to-end with the recipient epigastric vessels or with the circumflex deep inferior vessels, as second choice (Fig. 26.5). Microsurgical abdominal wall transplantation procedure added about 2 h to the operative time. The flap is then sutured in multiple layers to the recipient residual abdominal wall. First the deep fascia layer is sutured, and then the oblique muscles, subcutaneous tissues, and skin are sutured. The patient is dressed leaving a window to allow continuous monitoring of flap vitality. Monitoring consists in a clinical follow-up considering capillary reflow and flap temperature. Skin biopsies are performed in the navel to monitor graft rejection every week for at least 1 month. Sutures are removed after 15 days (Fig. 26.6).

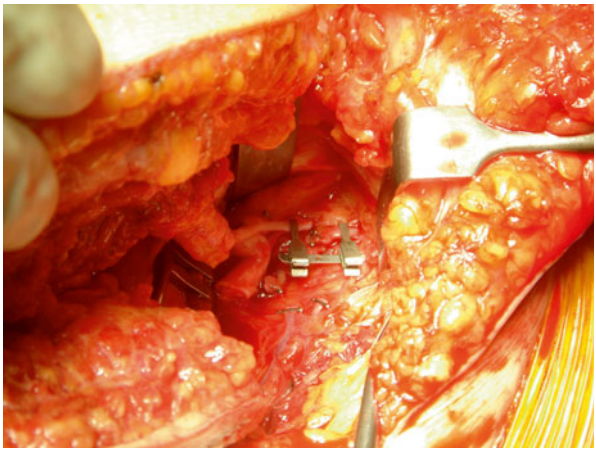

Fig. 26.5 End-to-end anastomosis between the graft pedicle and recipient epigastric inferior vessels

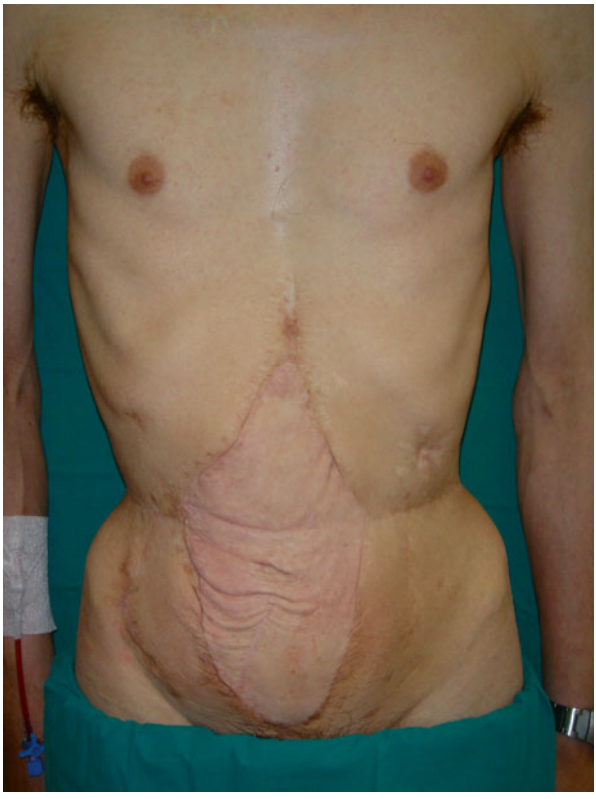

Fig. 26.6 Result after 4 years from abdominal wall transplantation

26.4 Discussion

Primary abdominal closure after intestinal or multivisceral transplantation is often impossible: the candidates to these transplantations have undergone multiple intestinal resections and present therefore a heavily scarred abdominal wall; moreover the abdominal cavity is often a virtual space [1, 9].

Another factor precluding a primary abdominal closure may be donor–recipient size mismatch. Fishbein et al. [10] reported that the most acceptable donor–recipient weight ratio is between 1.1 and 0.76, meaning that, ideally, donor and recipient sizes should be kept as close as possible. Several previous laparotomies and of partial/total enterectomy were predictive of difficult closure of the abdomen, even if the reported ratio is respected.

On the other hand, any attempt to close under tension might result in a wide range of complications, such as wound dehiscence, infections, necrosis of bowel loops, vascular thrombosis of the graft, abdominal compartment syndrome, and respiratory complications [4].

In such cases abdominal wall closure can be achieved with several methods: methods to reduce the graft volume, use of prosthetic mesh, previous abdominal wall expansion, pedicled flap, negative pressure therapy and subsequent skin graft, free flap, and abdominal wall transplantation.

There are several intraoperative maneuvers that can be performed routinely to reduce the graft volume and help achieve primary fascial closure.

Successful abdominal wall closure is most often obtained using donor that are 50–100 % the size of the recipient according to body weight. Overresuscitation with fluids should be avoided, and colloid solutions should be used if possible. Moreover all dysfunctional remnant bowels should be removed, and all adhesions should be lysed to completely develop all potential intraperitoneal space. Other space-creating options include splenectomy. However, caution is warranted because inferior outcomes were reported in recipients undergoing splenectomy mainly attributable to death from posttransplant sepsis.

Another method to assist with size discrepancy is a partial resection of transplanted intestine. However, it is important to leave children with a significant length of donor intestine that provides an ample margin for adequate absorption and function. If partial enterectomy is performed, it is better to resect the midportion of the bowel, leaving proximal jejunum and distal ileum for physiologic reasons.

A prosthetic mesh can be considered if the abdominal wall defect is partial: it provides satisfactory control of size discrepancy and protects the bowel from external injuries. The wound is left temporarily open over the mesh, with a dressing, and the mesh can represent a bridge for a definitive closure primarily or by a pedicled flap or alternative solutions, to be performed when the edema is reduced. The prosthetic material allows a quick recovery, but unfortunately it may present two important complications: infections of the mesh and formation of enterocutaneous fistulae [11].

Another option can be the pretransplant placement of intra-abdominal tissue expanders or peritoneal dialysis catheters for the expansion of the intra-abdominal

cavity by progressive instillation of fluid. Neither of these techniques demonstrated to be a good option. First of all, timing is very difficult, as it is impossible to foresee the availability of donor organs that are in critical short supply. Second, most of these patients have had multiple prior abdominal operations and present extensive intra-abdominal adhesions. Third, many candidates to multivisceral transplantation present portal hypertension; therefore, they are at high risk for pretransplant operations. Last, the use of foreign bodies is at risk for pretransplant infections.

Pedicled flap closure is possible with the collaboration of a plastic and reconstructive surgeon: it allows one stage closure avoiding the placement of alloplastic materials, but it is associated with longer operative time and an additional donor site wound. The pedicled anterolateral thigh (ALT) flap is the gold standard allowing the repair of medium- and large-sized defects [12]. ALT flap is a fasciocutaneous or cutaneous flap from the thigh, supplied by perforators of the descending branch of the lateral circumflex femoral artery, a branch of profunda femoris artery. The flap receives its blood supply through perforators (it is a perforator flap), musculocutaneous or septocutaneous, the former being the more common. The usefulness of the ALT flap for abdominal wall reconstruction was first reported by Kimata et al. in 1999 [13] in a series of four free flaps and three pedicled flaps. Its use as a pedicled flap has become very popular for abdominal wall reconstructions as it does not require microsurgical anastomosis. Moreover, the wide arc of rotation and long pedicle allow to reconstruct even proximal abdominal defects, and the fascia lata can be incorporated to prevent hernia formation [14]. The pivot point of the pedicled ALT flap is approximately 2 cm below the inguinal ligament, corresponding to the origin of lateral circumflex femoral artery [15]. The cutaneous territory of the flap extends from the greater trochanter to above the patella and involves more than half of the circumference of the thigh [16]. The donor site can be closed primarily or with a skin graft [17].

In our opinion, whenever possible, abdominal wall transplantation is the best option to overcome difficult closures [6].

It is a feasible and safe procedure: it allows primary closure of the abdomen, avoids the potential morbidity of exposed viscera, and permits early mobilization and rehabilitation of the patients.

Composite tissue allografts have become important tools for reconstructive surgeons. Face and hand transplantation allows incredible aesthetic and functional reconstructive results [18–20] but has the major drawback of requiring a lifetime immunosuppression.

As previously mentioned, abdominal wall defects can be repaired also using autologous flaps like pedicle anterolateral thigh flap [21, 22] or free flaps [23, 24], but these methods increase the operation morbidity because they prolong the operative time and produce a donor site wound. On the other hand, the patients undergoing intestinal or multivisceral transplantation are anyway administered lifetime immunosuppression; therefore, they are perfect candidates for composite tissue allotransplantation.

In Levi's first description, the abdominal wall transplant was vascularized by iliac vessels harvested bilaterally with a short segment of distal aorta and inferior cava vein from the donor. The removal of these pedicles deprives vascular surgeons of useful vascular grafts; therefore, microsurgical technique was proposed to preserve the donor's iliac vessels (Fig. 26.7).

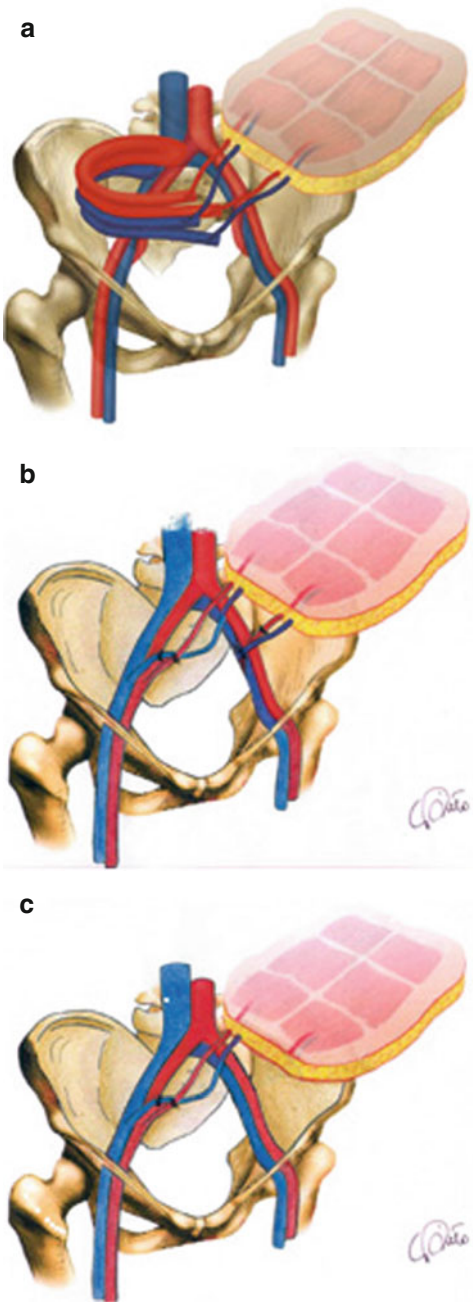

Fig. 26.7 Comparison between Levi's technique (**a**) [1] and microsurgical technique of flap revascularization based on bilateral (**b**) or monolateral (**c**) deep inferior epigastric pedicles anastomosis

Microsurgical technique allows to harvest in the same operative time an abdominal flap without impairment to other organs or pedicles, without vascular complications, saving the donor's iliac vessels to use as vascular grafts.

The collaboration with reconstructive surgeons expert in microsurgery is needed to perform abdominal wall transplantation with the same operative time as Levi's technique (2 h) and without increasing the risk of vascular thrombosis.

If the collaboration with an expert microsurgeon is not possible in our opinion, Levi's technique needs to be preferred.

If we compare the outcomes of the two different techniques, we can state that with Levi's technique a reversible cutaneous rejection was reported in four patients and three vascular complications with loss of the graft (on 14 patients), while with our microvascular technique no cutaneous rejection episodes nor vascular complications were observed on five patients [25].

Transplantation of the abdominal wall composite tissue allograft can take place during the intestinal transplant procedure or several days later with a graft from a different donor. Delaying implantation of the abdominal wall graft allows perioperative edema to diminish before abdominal closure and the patient's condition to stabilize. This strategy may be preferable when the recipient has a particularly large defect in the abdominal wall.

At the moment abdominal wall transplantation has always been used as a coverage flap allowing good aesthetic results. In literature there is not any report of successful reinnervation of the abdominal graft muscles that is definitely advisable in the future, in order to improve in the long term the organs contention and patient's every day activities.

References

1. Zanfi C, Cescon M, Lauro A, Dazzi A, Ercolani G, Grazi GL, Del Gaudio M, Ravaioli M, Cucchetti A, La Barba G, Zanello M, Cipriani R, Pinna AD. Incidence and management of abdominal closure-related complications in adult intestinal transplantation. Transplantation. 2008;85:1607–9.
2. Berli JU, Broyles JM, Lough D, Shridharani SM, Rochlin D, Cooney DS, Lee WP, Brandacher G, Sacks JM. Current concepts and systematic review of vascularized composite allotransplantation of the abdominal wall. Clin Transplant. 2013;27(6):781–9. doi:10.1111/ctr.12243. Epub 2013 Sep 16.
3. Alexandrides IJ, Liu P, Marshall DM, Nery JR, Tzakis AG, Thaller SR. Abdominal wall closure after intestinal transplantation. Plast Reconstr Surg. 2000;106(4):805–12.
4. Oikawa K, Ohkohchi N, Kato H, Orii T, Shimaoka S, Kawagishi N, Asakura T, Takayama J, Satomi S. Graft weight/recipient body weight ratio (G/R ratio) in living-related liver transplantation for pediatric patients: abdominal wall closure in cases with a large G/R ratio. Transplant Proc. 1998;30(7):3209–10.
5. Levi DM, Tzakis AG, Kato T, Madariaga J, Mittal NK, Nery J, Nishida S, Ruiz P. Transplantation of the abdominal wall. Lancet. 2003;361:2173.
6. Cipriani R, Contedini F, Santoli M, Gelati C, Sgarzani R, Cucchetti A, Lauro A, Pinna AD. Abdominal wall transplantation with microsurgical technique. Am J Transplant. 2007;7(5):1304–7. Epub 2007 Apr 8.
7. Starzl TE, Miller C, Broznick B, et al. An improved technique for multiple organ harvesting. Surg Gynecol Obstet. 1987;165:343–8.
8. Tzakis AG, Kato T, Nishida. Campath-1H in intestinal and multivisceral transplantation: preliminary data. Transplant Proc. 2002;34:937.
9. Carlsen BT, Farmer DG, Busuttil RW, Miller TA, Rudkin GH. Incidence and management of abdominal wall defects after intestinal and multivisceral transplantation. Plast Reconstr Surg. 2007;119(4):1247–55; discussion 1256–8.

10. Fishbein TM, Bodian CA, Miller CM. National sharing of cadaveric isolated intestinal allografts for human transplantation: a feasibility study. Transplantation. 2000;69(5):859–63.
11. Di Benedetto F, Lauro A, Masetti M, Cautero N, De Ruvo N, Quintini C, Diago Uso' T, Romano A, Dazzi A, Ramacciato G, Cipriani R, Ercolani G, Grazi GL, Gerunda GE, Pinna AD. Use of prosthetic mesh in difficult abdominal wall closure after small bowel transplantation in adults. Transplant Proc. 2005;37(5):2272–4.
12. Song YG, Chen GZ, Song YL. The free thigh flap: a new free flap concept based on the septocutaneous artery. Br J Plast Surg. 1984;37:149e59.
13. Kimata Y, Uchiyama K, Sekido M, et al. Anterolateral thigh flap for abdominal wall reconstruction. Plast Reconstr Surg. 1999;103:1191e7.
14. Ng RW, Chan JY, Mok V, Li GK. Clinical use of a pedicled anterolateral thigh flap. J Plast Reconstr Aesthet Surg. 2008;61(2):158–64.
15. Friji MT1, Suri MP, Shankhdhar VK, Ahmad QG, Yadav PS. Pedicled anterolateral thigh flap: a versatile flap for difficult regional soft tissue reconstruction. Ann Plast Surg. 2010;64:458–61.
16. Evriviades D, Raurell A, Perks GB. Pedicled anterolateral thigh flap for reconstruction after radical groin dissection. Urology. 2007;70:996–9.
17. Yildirim S, Gideroglu K, Akoz T. Anterolateral thigh flap: ideal free flap choice for lower extremity soft-tissue reconstruction. J Reconstr Microsurg. 2003;19:225e33.
18. Devauchelle B, Badet L, Lengelé B, et al. First human face allograft: early report. Lancet. 2006;368(9531):203–9.
19. Lierde KM, Roche N, Letter MD, et al. Speech characteristics one year after first Belgian facial transplantation. Laryngoscope. 2014;124(9):2021–7.
20. Carty MJ, Hivelin M, Dumontier C, et al. Lessons learned from simultaneous face and bilateral hand allotransplantation. Plast Reconstr Surg. 2013;132(2):423–32.
21. Kimata Y, Uchiyama K, Sekido M, et al. Anterolateral thigh flap for abdominal wall reconstruction. Plast Reconstr Surg. 1999;103(4):1191–7.
22. Lannon DA, Ross GL, Addison PD, Novak CB, Lipa JE, Neligan PC. Versatility of the proximally pedicled anterolateral thigh flap and its use in complex abdominal and pelvic reconstruction. Plast Reconstr Surg. 2011;127(2):677–88.
23. Baumann DP, Butler CE. Soft tissue coverage in abdominal wall reconstruction. Surg Clin N Am. 2013;93(5):1199–209.
24. Ninković M, Kronberger P, Harpf C, et al. Free innervated latissimus dorsi muscle flap for reconstruction of full-thickness abdominal wall defects. Plast Reconstr Surg. 1998;101(4):971–8.
25. Berli JU, Broyles JM, Lough D, Shridharani SM, Rochlin D, Cooney DS, Lee WP, Brandacher G, Sacks JM. Current concepts and systematic review of vascularized composite allotransplantation of the abdominal wall. Clin Transplant. 2013;27(6):781–9.

Anesthetic and Perioperative Management for Intestinal Transplantation

27

Antonio Siniscalchi, Lorenzo Gamberini, and Stefano Faenza

27.1 Preoperative Evaluation of Small Bowel Transplant Candidates

27.1.1 Clinical and Laboratory Evaluation

Most patients with irreversible intestinal failure have considerable comorbidities; hence, they are rigorously pre-assessed by a multidisciplinary team to establish cardiovascular fitness, risk profile, and vascular access strategy. Chronic treatment with TPN may result in chronic vascular thrombosis at various access sites. For this reason, the evaluation of venous access with venous Doppler studies and venous angiography is particularly important during the initial assessment of the patient, because it helps avoiding as much as possible a long and distressing search for a vein in the operating room, which can result in a delay of the start of the procedure and a potential increase of the ischemia time of the graft. Laboratory evaluation for intestinal failure includes complete blood count; assessment of metabolic, acid–base, fluid, electrolyte, and coagulation status (antithrombin III-deficient patients are more likely to suffer from perioperative thrombotic events); as well as standard liver and

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renal function tests [1]. Testing of the patient's cardiopulmonary status should include electrocardiogram and chest radiography. A 2D echocardiogram is helpful to screen for gross abnormalities, and if clinically indicated, pulmonary function studies and a dobutamine stress echocardiography should be considered [2, 3].

27.1.2 Monitoring

Routine monitoring with ECG, oxygen saturation, and noninvasive blood pressure is established before the induction of anesthesia. Two large-bore cannulas and preferably two separate arterial lines are inserted. Pulmonary artery flotation catheters, esophageal Doppler, PiCCO, LIDCO, and transesophageal echocardiography are all used in different centers. Transesophageal echocardiography (TEE) is the first choice in patients with thrombosis of the upper circulation. It allows a noninvasive assessment of myocardial function and aids in the management of the patient's volume status (fluid volume and inotrope drugs titration). Early diagnosis of thromboembolic events is another advantage of this technique [4]. Pulse contour analysis for measurement of cardiac output (PiCCO) is another less invasive modality than pulmonary arterial catheterization. This device enables also the assessment of intravascular blood volume and therefore guides correct intraoperative fluid management [5]. Coagulation monitoring is best provided by thromboelastogram (TEG) although platelet count, activated prothrombin time, thromboplastin time, fibrinogen, and fibrinogen decay products can also supply information and guide reintegration therapy [4].

27.2 Intraoperative Management of Small Bowel Transplantation

27.2.1 Anesthetic Induction and Maintenance

Meticulous positioning of the patient on the operating table is mandatory. The patient is positioned supine with both arms either carefully positioned at the patient's side or one or both arms abducted to a maximum of 70° to protect against brachial plexus injury. Maintaining normothermia represents a major challenge. Warm air convection heating blankets are positioned below and above the patient, with the lower chest and abdomen exposed for surgical access. Thromboembolic deterrent stockings and calf compression devices should be considered, as these patients are at increased risk of thromboembolic complications, but should be removed during the anastomotic phase when the aorta is partially clamped. Anesthesia typically begins with a rapid sequence induction, which is made necessary by the emergent nature of the surgery. An arterial catheter is placed either before or shortly after induction; continuous five-lead electrocardiography monitoring, pulse oximetry, capnography, and end-tidal gas analysis, and esophageal temperature are the minimum monitoring for patients undergoing intestinal transplantation. Following induction, a broad-spectrum antibiotic is administered; a nasogastric tube is inserted

and carefully secured as postoperative displacement would require replacement under direct vision because of the risk of anastomotic disruption. Generally the patients are orally intubated and ventilated with anesthesia-integrated machine and with minimal flow technique. A balanced technique is used for maintenance of anesthesia with a volatile agent, narcotic, and nondepolarizing muscle relaxant. Nitrous oxide is best avoided as it can make surgery more difficult by inflating the intestines and increasing the risk of visceral damage. The effects of the anesthetic technique used on patient outcomes are unknown. At the author's center, a balanced anesthesia is used. This typically consists of a volatile agent in low to moderate concentrations (0.5–1.0 minimum alveolar concentration [MAC]) to ensure unconsciousness, while an opioid, usually fentanyl, is chosen to blunt the sympathetic response to stimulation and to provide a smooth transition to the postoperative period. If the patient has some degree of renal dysfunction, the active metabolites of meperidine (normeperidine) can accumulate, as well as the active metabolites of morphine (morphine-6- and morphine-3-glucuronide), which may cause prolonged sedation postoperatively [6]. Short-acting opioids with extrahepatic metabolism, such as remifentanil, may be considered for intraoperative analgesia [7–9]. A protective lung ventilation strategy should be used, targeting tidal volumes of 6–8 mL kg^{-1}, with minimal positive end-expiratory pressure. Surgical retraction can lead to a significant increase in airway pressures. Most induction agents can be used. Propofol is a safe choice [10, 11], but etomidate might be preferable in cardiovascularly unstable patients. In case of encephalopathy, benzodiazepines should be avoided, and the use of high-dose opioids must be limited. If hepatic or renal dysfunction exists, muscle relaxants, which are not metabolized by the liver and do not rely on renal excretion, such as atracurium and cisatracurium, are superior choices. Cisatracurium may be the preferred neuromuscular blocking agent in patients with liver failure, because of its organ-independent elimination and diminished histamine release. Succinylcholine could be administered in the absence of hyperkalemia, but rocuronium and mivacurium are safe alternatives for rapid sequence induction [9]. According to the currently available evidence, in small bowel transplantation, insertion of a pulmonary arterial catheter is usually justified by the presence of an underlying cardiac dysfunction, while the fluid status can be easily monitored by the measurement of the central venous pressure. The transesophageal echocardiography (TEE) is a technique that is increasingly being used during the procedure. Some intestinal transplant sites avoid pulmonary artery catheter insertion when TEE is used, although the pulmonary artery catheter may be necessary when continuous intraoperative monitoring of pulmonary artery pressures is desired or for postoperative hemodynamic and fluid management in the intensive care unit (ICU). Postoperative analgesic strategy is provided by either a patient-controlled analgesia or a patient-controlled epidural analgesia. Bupivacaine or ropivacaine administration is safe in clinically relevant doses [12, 13]. Careful consideration must be given to the insertion of an epidural catheter to provide postoperative analgesia. Epidural vasodilatation can potentially trigger episodes of hypovolemia and cardiovascular instability. Moreover, it is not uncommon that intestinal transplanted patients develop a significant degree of coagulopathy during the perioperative

period. However, the use of epidurals may facilitate earlier extubation, reduce the risk of respiratory and thromboembolic complications, and potentially provide superior postoperative analgesia. Therefore, the risk benefit balance must be thoroughly evaluated for every single patient regarding the use of this technique.

27.2.2 Intraoperative Management: Preenterectomy Stage

This phase of surgery starts with an extended bilateral subcostal incision, with a cranial and caudal midline extension, and ends with cross-clamping of the superior mesenteric artery (SMA), the superior mesenteric veins (SMV), and the inferior vena cava (IVC). This phase involves the dissection and mobilization of the intestine and the identification of the vessels; hypovolemia should be treated in an anticipatory fashion with colloid-containing fluid to minimize changes in preload. Routine monitoring should include regular arterial blood gases, with evaluation of sodium, potassium, calcium, hemoglobin, hematocrit, glucose, and lactate. Blood loss may be significant if the mesenteric and portal veins are thrombosed and if there is a history of previous surgery, with peritoneal adhesions, or portal hypertension. Crystalloids are used to maintain CVP in the range of 8–12 mmHg; the use of albumin is justified only if the measured serum albumin is low. However, the end point of the treatment of any volemic imbalance is not the CVP value, but the combination of several factors that have to be evaluated by the anesthesiologist during surgery, including the appearance of the surgical field (vessels and visceral organs, blood loss), the urinary output, the central and systemic blood pressure curves, and their changes during the ventilatory cycle. The use of blood and fluid warmers, a warming blanket, and a forced-air warming unit is necessary to maintain patient temperature. Core temperature generally decreases until graft reperfusion and increases thereafter. A fall of 0.5 °C in the patient's temperature may be observed after the cold intestinal graft has been placed in the abdominal cavity, and a further acute fall is associated with graft reperfusion. Hemodynamic stability has the double effect of keeping the recipient in a physiologic condition and ensuring adequate perfusion to the graft. Multiple previous abdominal surgical procedures can prolong substantially the dissection of the native intestine, potentially increasing the intraoperative transfusion requirements and the need for an adequate supply of blood. Patients with normal liver function receiving isolated intestinal grafts have a normal preoperative coagulation status, and the administration of fresh frozen plasma, coagulation factors, and platelets is only justified by the volume of blood loss. Also in our experience, as expected, blood requirements were not significant during SBT, especially in comparison with liver transplantation, and the same was observed for the other blood products. Intraoperative coagulation is guided by TEG and observation of the surgical field. In patients with hepatic failure receiving also a short bowel transplant, it is possible to observe quite dramatic intraoperative TEG changes due to coagulation abnormalities, but a severe coagulopathy is rare, and the number of samples required for a safe TEG monitoring is lower in comparison to liver transplantation.

27.2.3 Intraoperative Management: Enterectomy Stage

The enterectomy stage begins with the occlusion of vascular inflow to the intestine and ends with the graft reperfusion. Cross-clamping of the inferior vena cava and manipulation can decrease the venous return to the heart and cause hypotension. Endotoxins can be released from localized abdominal infections causing additional cardiovascular instability. The fluid infusion may be increased to keep CVP in the desired range, the volatile agent concentration may be decreased in the inspired oxygen/air mixture, and vasopressors such as ephedrine and adrenaline may be administered before caval clamping. It must be remembered that the time frame of the surgical maneuver is an important variable; often the reversal of the hemodynamic imbalance and of the hypotension is a matter of waiting short time and not to overtreat. Frequent monitoring of blood gases and acid–base, electrolyte, hematocrit, coagulation, metabolic, and hemodynamic status is necessary for optimal management in this stage.

27.2.4 Intraoperative Management: Neointestinal Stage

Reperfusion of the new intestine through the mesenteric vessels begins the neointestinal stage. Often in isolated small bowel transplantation, the superior mesenteric artery (SMA) of the graft is anastomosed to the SMA of the recipient, and the same is done between the superior mesenteric veins (SMV). In other patients undergoing SBT, SMA is anastomosed to the aorta and SMV is anastomosed to the inferior vena cava. Some anastomotic variations are often possible; in our experience, patients in whom the intestinal transplant consisted of a modified multivisceral variant excluding the donor liver had 2 cm of the donor thoracic aorta anastomosed end to side to the suprarenal aorta. Next, a Carrl's patch including both the celiac trunk and the SMA was anastomosed to the aortic graft. Finally, the graft portal vein was anastomosed in an end-to-side fashion. The distal aorta of the donor is closed with a piece of artery obtained from the proximal thoracic aorta of the donor as a "hatch." In a small bowel and liver and multivisceral transplant, a higher incidence of reperfusion-associated syndrome, similar to that seen during liver transplantation, can be expected. Reperfusion effects may be reduced following a portal anastomosis, because the flow through the liver can buffer the cardiac effect of the cold splanchnic fluid, while the declamping of a caval anastomosis cannot enjoy such a protective mechanism. Reperfusion is associated with abrupt increases in potassium and hydrogen ions concentration, an increase in preload, and a decrease in systemic vascular resistance and blood pressure. Hypothermia, monitored through a centrally placed catheter, is a marker for the presence of graft outflow into the central circulation. Life-threatening hyperkalemia, clinically detectable by changes in the ECG, requires prompt treatment. Calcium chloride and sodium bicarbonate are the drugs of choice for the acute treatment of hyperkalemia. A "postreperfusion syndrome" characterized by marked hypotension and cardiovascular instability occurs in 47 % of small bowel transplants [14]. Therefore, it is imperative that before reperfusion, the cardiovascular status of

the patient is fully optimized, and infusions of appropriate fluids and vasoactive agents are readily available. A retrospective study of 27 patients who underwent SBT showed significant decreases in mean arterial pressure and systemic vascular resistance after reperfusion, associated with minor changes in mean arterial pulmonary arterial pressure, central venous pressure, and wedge pressure [15]. However, systemic vascular resistance and mean arterial pressure decreased only about 30 % from baseline at approximately 30 min after reperfusion and continued to remain low throughout the procedure. Cardiac index appeared to be well preserved as indicated by the slight increase in value, signifying that SBT was not associated with cardiac dysfunction. In this study, the authors showed a hypocoagulative pattern, as evaluated by TEG, probably caused by surgical stress, blood loss, and hemodilution. The metabolic changes that commonly occur during SBT result from ischemia–reperfusion injuries to the donor intestine. The intestinal damage due to ischemia and cold storage is exacerbated by a variety of biochemical/immunological processes in the immediate postreperfusion period after revascularization. In this observational study, PRS was considered when the mean arterial blood pressure was 30 % lower than the pre-unclamping value and lasted for at least 1 min within 10 min after unclamping. In these patients undergoing SBT, the duration of cold ischemia and preoperative glomerular filtration rate were independent predictors of postreperfusion syndrome (PRS), and the occurrence of intraoperative PRS was associated with significantly more frequent postoperative renal failure and with more frequent early postoperative death.

Table 27.1 synthesizes the main intraoperative tips of anesthesiologic management for every phase of the intervention.

27.3 Postoperative Care of the Intestinal Transplant Patient

27.3.1 Allograft Rejection

Routine surveillance endoscopy via the ileostomy, with random biopsies, is performed twice a week for the first month after transplant. This procedure enables the diagnosis of rejection prior to the manifestation of clinical signs and symptoms. For the subsequent 1–2 months, endoscopy and biopsies are performed every week. Indications for biopsies include unexplained fever, change in stoma output or appearance, gastrointestinal bleeding, and skin rash. Gross appearance of the mucosa does not correlate with the histologic findings, but endoscopy with biopsy remains the gold standard for diagnosis of rejection in the intestinal allograft. The diagnosis of rejection is based on pathologic criteria: apoptosis, cryptitis, and exfoliation. Unfortunately, these findings can also be present in infectious enteritis [16, 17].

Stomal output increases rapidly after the first few hours and may reach several liters a day. Bicarbonate losses may be marked and need to be replaced if this causes metabolic acidosis. Diarrhea is common after SBT and is often multifactorial in origin. Denervation of the grafted small bowel is probably the major cause of diarrhea, but other causes include ischemia–reperfusion injury, rejection, graft-versus-host disease, and CMV enteritis. Fecal calprotectin assays might help in the early diagnosis

Table 27.1 Main intraoperative tips for anesthesiologic management for every phase of the intervention

Anesthetic induction and maintenance	Preenterectomy stage	Enterectomy stage	Neointestinal stage
Routine monitoring electrocardiography pulse oximetry, capnography, temperature, invasive arterial blood pressure, baseline arterial blood gas 8 F or larger cannulas into the peripheral vein Connect to a rapid infusion system (500–1,500 mL/min)	CVP 8–12 mmHg Maintain Hgb >10 g/dl Norepinephrine to keep mean blood pressure >60 mmHg	Maintain Hgb >8 g/dl IV fluids to keep CVP around 8–12 mmHg Adrenaline/ norepinephrine to preserve blood pressure >60 mmHg and CO >5 L/min	Maintain Hgb >8 g/dl IV fluids to keep CVP around 8–12 mmHg IV adrenaline 10/20 mcg bolus to keep BP>60 mmHg Adrenaline/ norepinephrine to preserve blood pressure >60 mmHg and CO >5 L/min
Rapid sequence induction of anesthesia Fentanyl 1–2 μg/kg, propofol 0.5–2 mg/kg, cisatracurium 0.5–1.0 mg/kg Maintain anesthesia balanced with minimal flow, low tidal volume (6–8 mL/Kg), positive end-expiratory pressure 5–8 cm H_2O if necessary recruitment maneuvers	Infusion of albumin 20 % if severe hypoalbuminemia Correct metabolic acidosis, hypocalcemia, hypomagnesemia, glycemia, and hyperkalemia	Correct metabolic acidosis, hypocalcemia, hypomagnesemia, glycemia, and hyperkalemia	Correct metabolic acidosis, hypocalcemia, hypomagnesemia, glycemia, and hyperkalemia
Invasive monitoring using an 8.0-French pulmonary catheter into the right internal jugular vein Central venous access using an 8.0-French bilumen into the left internal jugular vein	Consider coagulation monitoring and correction if coexisting liver failure Consider elastic stockings for venous thromboembolism prevention	Consider coagulation monitoring and correction if coexisting liver failure	Consider coagulation monitoring and correction if coexisting liver failure Consider elastic stockings for venous thromboembolism prevention
Intravenous antibiotics			
Warmers	Warmers	Warmers	Warmers
Incision			

of rejection and can be used on an outpatient basis, particularly in those patients who have had their ileostomy closed, although the utility of this assay is restricted by significant interpatient variability [18, 19]. The role of citrulline as a quantitative marker of rejection is being investigated. Citrulline, a nonessential amino acid, is produced by the intestinal mucosa and is present in the serum. Citrulline levels reflect the functional absorptive capacity of the intestine. In patients with short gut syndrome, the postabsorptive plasma concentration of citrulline is not only a measure of functional absorptive bowel length but is also an indicator of permanent intestinal failure. In transplanted patients, plasmatic levels of citrulline decreased during rejection and returned to prerejection levels upon successful treatment of rejection, and the severity of rejection inversely correlated with citrulline levels.

27.3.2 Infection

The postoperative care of intestinal transplanted patients is complicated by their markedly debilitated state, balanced immunosuppressive regimens to prevent rejection, and the necessity to prevent and treat infection. The primary treatment goal is to maximize benefits while minimizing the morbidity of immunosuppressive agents. A natural consequence of transplantation of an organ exposed to external microorganisms in the presence of profound immunosuppression is the susceptibility of the recipient to local and systemic infections. Gastrointestinal decontamination is required in small bowel transplantation and puts the patient at a very high risk of CMV new infection or reactivation. Every patient is therefore treated (except when donor and recipient are both CMV negative), according to this protocol: D+/R− requires ganciclovir plus specific anti-CMV Ig, and D+/R+ or D−/R+ needs to be treated with ganciclovir 5 mg/kg i.v. two times a day until the patient can receive 1 g×3 per os up to 3–4 months postoperatively. A major advance in the reduction of graft failure and patient mortality has been introduced by improved diagnosis, prophylaxis, and therapy of viral infections and their complications. Routine use of polymerase chain reaction (PCR) assay for early viral detection has greatly reduced the adverse influence of this virus. Monitoring Epstein–Barr virus (EBV) by PCR, which might be a prelude posttransplant lymphoproliferative disease (PTLD) [20], enables the reduction of immunosuppression or, in advanced cases, the use of the anti-CD20 monoclonal antibody, rituximab. The presence of rising EBV titers on routine surveillance often provides a trigger to reduce the dose of maintenance immunosuppression by 25–50 %. PTLD which is refractory to these measures, recurrent or progressive, often requires chemotherapy as for non-Hodgkin's lymphoma [16].

27.3.3 Fluid and Nutrition Management

Fluid management is the major postoperative problem after small bowel and multiple organ transplantation because the fluid and electrolyte needs of the transplant recipient are highly variable. Fluid replacement is usually guided by the blood pressure,

right atrial pressure, pulmonary capillary wedge pressure, and urine output, but a reliable monitoring technique to determine volemia is needed. In the immediate post-transplant period, the graft is subject to mucosal sloughing secondary to ischemia–reperfusion injury, and the patient can lose large amounts of fluid through the graft. Preservation injury is however a relatively minor problem in intestinal transplantation because of the intestine's great capacity for epithelial regeneration. In addition, associated bicarbonate loss can be high. During episodes of rejection, the patient can also have exaggerated fluid losses that can lead to dehydration. Third-space fluid requirements can be massive, and inadequate replacement leads to end-organ dysfunction, particularly renal failure. Central venous pressure monitoring, preferably with pulmonary arterial catheterization, is essential as any other monitoring technique which can often be a reliable picture of body volume distribution. Several liters of fluid may be required in the initial 24–48 h postoperatively simply to maintain central pressures adequate to provide a satisfactory urine output. During this time, the patients may develop extensive peripheral edema, which dissipates over the next few days as the fluids are mobilized and requirements stabilize. This phenomenon occurs after all abdominal surgery, but these patients have significantly greater fluid shifts than do patients undergoing major non-transplantation abdominal surgery. However, continued increases in fluid requirements may herald infection or rejection. The aim is to commence enteral feeding as early as possible after transplantation. Ileus usually persists for the first few postoperative days as ischemia–reperfusion injury resolves [21]. Most centers introduce enteral intake between 3 and 7 days postoperatively, with some waiting until stomal output is demonstrated. Typically, a small volume (10 mL/h) of non-elemental feeds is started initially; the aim is to provide all nutritional requirements enterally, with complete withdrawal of parenteral nutrition within 4–6 weeks. This early transition enhances graft adaptation and minimizes postoperative complications. Initially, feeding is given via an enteral tube. Because gastric emptying is delayed early after transplantation, jejunal feeding is the preferred route, most commonly via a jejunostomy, fashioned at the time of the transplant. Some units use nasojejunal tubes [16]. Transition to oral diet is individualized as tolerated and tends to occur more rapidly in adults than children. Up to 45 % of children have continued to require nasogastric tube feeding at 2 years; factors such as food aversion, high relative fluid and energy requirements, and prior adverse dietary experiences with a tendency to anorexia often contribute to delayed transition. Enteric lymphatics are often disrupted during surgery, with recovery often taking weeks to months. Chylous ascites might develop and require repeated paracentesis over a period of weeks.

In the event of this complication, most centers prefer a low-dose lipid formulation (1 g/kg or 1 g/100 mL feed) initially, with or without medium chain triglycerides; these are absorbed via the portal circulation, rather than lymphatics [21]. Patients are also informed to avoid a high intake of simple carbohydrates and sugars, such as those contained in fruit, fruit juices, and soft drinks, as these can cause osmotic diarrhea. Monitoring of nutritional parameters is vital, not only as the transition to oral intake occurs but also in the long term. Supplementation with fat-soluble vitamins A, D, and E is often required. Iron studies, B12, zinc, and selenium levels are other important nutrients to monitor.

References

1. Casella JF, Lewis JH, Bontempo FA, Zitelli BJ, Markel H, Starzl TE. Successful treatment of homozygous protein C deficiency by hepatic transplantation. Lancet. 1988;1:435–8.
2. Williams K, Lewis JF, Davis G, Geiser EA. Dobutamine stress echocardiography in patients undergoing liver transplantation evaluation. Transplantation. 2000;69:2354–6.
3. Giraldo M, Martin D, Colangelo J, Bueno J, Reyes J, Fung JJ, et al. Intestinal transplantation for patients with short gut syndrome and hypercoagulable states. Transplant Proc. 2000;32:1223–4.
4. Faenza S, Arpesella G, Bernardi E, Faenza A, Pierucci E, Siniscalchi A, et al. Combined liver transplants: main characteristics from the standpoint of anesthesia and support in intensive care. Transplant Proc. 2006;38:1114–7. doi:10.1016/j.transproceed.2006.02.018.
5. Della Rocca G, Costa GM, Coccia C, Pompei L, Di Marco P, Pietropaoli P. Preload index: pulmonary artery occlusion pressure versus intrathoracic blood volume monitoring during lung transplantation. Anesth Analg. 2002;95:835–43, table of contents.
6. Hanna MH, D'Costa F, Peat SJ, Fung C, Venkat N, Zilkha TR, et al. Morphine-6-glucuronide disposition in renal impairment. Br J Anaesth. 1993;70:511–4.
7. Park GR, Evans TN, Hutchins J, Borissov B, Gunning KE, Klinck JR. Reducing the demand for admission to intensive care after major abdominal surgery by a change in anaesthetic practice and the use of remifentanil. Eur J Anaesthesiol. 2000;17:111–9.
8. Bito H, Ikeuchi Y, Ikeda K. Effects of low-flow sevoflurane anesthesia on renal function: comparison with high-flow sevoflurane anesthesia and low-flow isoflurane anesthesia. Anesthesiology. 1997;86:1231–7.
9. Smith CE, Hunter JM. Anesthesia for renal transplantation: relaxants and volatiles. Int Anesthesiol Clin. 1995;33:69–92.
10. Toivonen HJ. Anaesthesia for patients with a transplanted organ. Acta Anaesthesiol Scand. 2000;44:812–33.
11. Goldman LJ, Santamaría ML, Gámez M. Anaesthetic management of a patient with microvillus inclusion disease for intestinal transplantation. Paediatr Anaesth. 2002;12:278–83.
12. Bodenham A, Park GR. Plasma concentrations of bupivacaine after intercostal nerve block in patients after orthotopic liver transplantation. Br J Anaesth. 1990;64:436–41.
13. Dauri M, Costa F, Servetti S, Sidiropoulou T, Fabbi E, Sabato AF. Combined general and epidural anesthesia with ropivacaine for renal transplantation. Minerva Anestesiol. 2003;69:873–84.
14. Planinsic RM. Anesthetic management for small bowel transplantation. Anesthesiol Clin N Am. 2004;22:675–85. doi:10.1016/j.atc.2004.06.007.
15. Siniscalchi A, Cucchetti A, Miklosova Z, Lauro A, Zanoni A, Spedicato S, et al. Post-reperfusion syndrome during isolated intestinal transplantation: outcome and predictors. Clin Transpl. 2012;26:454–600. doi:10.1111/j.1399-0012.2011.01530.x. n.d.
16. Horslen SP. Optimal management of the post-intestinal transplant patient. Gastroenterology. 2006;130:S163–9. doi:10.1053/j.gastro.2005.11.050.
17. Wu T, Abu-Elmagd K, Bond G, Nalesnik MA, Randhawa P, Demetris AJ. A schema for histologic grading of small intestine allograft acute rejection. Transplantation. 2003;75:1241–8. doi:10.1097/01.TP.0000062840.49159.2F.
18. Sudan D, Vargas L, Sun Y, Bok L, Dijkstra G, Langnas A. Calprotectin: a novel noninvasive marker for intestinal allograft monitoring. Ann Surg. 2007;246:311–5. doi:10.1097/SLA.0b013e3180f61af4.
19. Mercer DF, Vargas L, Sun Y, Moreno AMA, Grant WJ, Botha JF, et al. Stool calprotectin monitoring after small intestine transplantation. Transplantation. 2011;91:1166–71. doi:10.1097/TP.0b013e318215e709.
20. Wagner H-J, Cheng YC, Huls MH, Gee AP, Kuehnle I, Krance RA, et al. Prompt versus preemptive intervention for EBV lymphoproliferative disease. Blood. 2004;103:3979–81. doi:10.1182/blood-2003-12-4287.
21. Gupte GL, Beath SV. Update on intestinal rehabilitation after intestinal transplantation. Curr Opin Org Transplant. 2009;14:267–73. doi:10.1097/MOT.0b013e32832ac0f5.

Segmental Living-Related Small Bowel Transplantation

28

Ivo Tzvetanov, Giuseppe D'Amico, and Enrico Benedetti

28.1 Introduction

Small bowel transplantation (SBT) has provided effective therapy for the patients with chronic, irreversible intestinal failure affected by life-threatening complications of total parenteral nutrition [1].

Living donor segmental small bowel transplantation potentially can provide advantages, comparing to deceased donor, including better tissue compatibility, shorter cold ischemia time, ability to implement desensitization protocols, and better donor bowel preparation. Probably the biggest advantage is that intestinal transplantation from living donor is an elective procedure, which is done at the optimal time for the recipient.

The first clinical transplant from a living donor (LD) was reported in 1971. Alican et al. described the case of an 8-year-old boy with the resection of the small bowel from the ligament of Treitz to the ileocecal valve secondary to strangulation. The transplant was performed with approximately 3 ft of ileum transplanted from his mother. However, the recipient's procedure was complicated by thrombosis of the vena cava, and the allograft had to be subsequently removed on the ninth posttransplant day [2].

The introduction of cyclosporine distinctly changed the outcome for solid organ transplantation. Nonetheless, the use of cyclosporine did not have as much benefit for intestinal transplantation as it did for other transplanted solid organs. In the cyclosporine era, only two intestinal transplants from living donors were reported by Deltz et al. [3, 4], with both recipients receiving a 60 cm segment of jejunum. First recipient was a boy 4 years of age with volvulus, who received the graft from his mother;

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unfortunately, the graft was removed due to an intractable rejection episode. Second recipient was a 42-year-old woman with a subtotal small bowel resection secondary to the thrombotic occlusion of mesenteric veins. The patient was on full oral intake 2 weeks later and thereafter remained off parenteral nutrition until 1990, when chronic rejection caused the loss of the graft function. At that point in time, it was the first successful LD intestinal transplant with a long-term function of over 2 years.

The introduction of tacrolimus has allowed intestinal transplantation to become a clinically accepted procedure. Benedetti et al. during the 1990s studied the technical aspects of LD intestinal transplantation in a pig model [5]. Consequently, the same group performed the first LD intestinal transplant, from which they concluded: (1) the ileum was the best option due to its greater absorptive capacity of bile acids, vitamins, fat, and water; (2) the terminal ileum (20–30 cm), the ileocecal valve, and the cecum should remain in the donor to minimize morbidity; (3) a vascular pedicle should be used consisting of only one artery and vein (either the ileocolic artery and vein or the terminal branches of the superior mesentery artery (SMA) and superior mesentery vein (SMV); and (4) the bowel continuity should be restored with a proximal bowel anastomosis and a distal ileostomy (to allow access to graft biopsy) (6). After these two first successful LD intestinal transplants at the University of Minnesota, the group published the respective guidelines in 1997 [6], as a standardized technique for intestinal transplants.

Morris et al in 1995 described a LD intestinal transplant in an adult patient with a desmoid tumor, whose donor was his monozygotic twin. They transplanted the distal ileum, ileocecal valve, and portion of the cecum: however, as they also removed the terminal ileum of the donor, he became vitamin B12 deficient [7].

Fujimoto et al. [8] reported in 1998 the first LD intestinal transplantation in Japan. A 2.5-year-old boy who had been suffering from short bowel syndrome and recurrent line sepsis underwent SBT using a segmental graft from his mother. They resected her distal ileum (100 cm) out of her 460 cm of small intestine. The vessels were anastomosed to the recipient's infrarenal aorta and vena cava, respectively. The donor was discharged on postoperative day 15 without any surgical or medical complication. In 2004, Lee et al. [9] described the first experience at Catholic University of Korea, Seoul. The patient was a 57-year-old female with short bowel syndrome. A 150 cm distal ileum graft from a 27-year-old living-related donor was successfully transplanted; the graft vessels were anastomosed to the recipient's inferior mesenteric vessels. The donor and recipients recovered without complications.

Ishii et al. [10] reported in 2006 their experience of two cases of LD intestinal transplantation. The first patient was a 14-year-old boy with TPN-dependent short bowel syndrome associated with hypoganglionosis. The second patient was a 27-year-old female who had undergone massive enterectomy due to volvulus. Up to one third (150 cm in case 1, 210 cm in case 2) of the total small intestine was harvested from the ileum preserving 30 cm of terminal ileum proximal to the ileocecal valve. The vessels were connected to the recipient infrarenal aorta and inferior vena cava. Both donor experienced no complications and were discharged at 10 days after the operation. The two recipients did not have any surgical complications.

Benedetti et al. in 2011 documented their experience with six combined intestinal/liver transplants at the University of Illinois Hospital [11]. The transplants were

performed between 2004 and 2007, with a total of six children (average age 13.5 months) having received the grafts from one of their parents. Three of these recipients had a simultaneous transplantation, while the other three recipients had a staged procedure, with an average interval of 6 days based on hemodynamic stability after the liver graft was implanted.

None of the donors had any perioperative mortality or morbidity; all donors were discharged home on a regular diet. Five of the six children are still alive with adequate graft function, whereas one recipient died due to plasmablastic lymphoma, albeit with functioning graft.

TPN-associated complications, such as lack of vascular access, recurrent line infections, and liver failure, continue to become life-threatening. If it is taken into account that the pediatric population is more prone to liver disease and life-threatening complications secondary to TPN, then LD intestinal grafts could prevent the progression to end-stage liver disease and be considered lifesaving when a deceased donor (DD) graft is not available. Thus, the main goals of LD intestinal transplantation are to improve posttransplant outcomes and to decrease the mortality on the waiting list by reducing the patients waiting time.

28.2 Donor

In order to minimize the incidence of complications and increase the rate of success, it becomes necessary to choose the donor carefully. Table 28.1 summarizes the required workup for living-related donor evaluation for LD intestinal transplant. The technical aspects of LDIT were standardized by Gruessner and Sharp in 1997, as was previously described.

Table 28.1 Donor evaluation

Flowchart for donor evaluation
Comprehensive analysis of medical and surgical history, review of systems, physical examination, current medications, history of malignancy, and previous intestinal surgery
ABO compatibility, HLAa type, lymphocytotoxic crossmatch
Comprehensive metabolic panel, vitamins A, D, E, K, and B12
Prothrombin time, partial thromboplastin time, alpha-fetoprotein, ammonia
Chest X-ray, electrocardiogram
Serology (CMV, EBV, VZV, HIV, HCV, HBeAg, HBsAg, HBsAbb), complete blood count. Urine and stool cultures
Anesthesia history, surgical procedures, and drug allergies
Psychiatry evaluation, social work consultation
An interview with a member of the institutional ethics committee to discuss with the potential donor about motivations an understanding of the risk involved
CT scan of the abdomen or 3D-angio-CT scan

Source: Data from Ref. [11]

aHLA histocompatibility leukocyte antigen, *bCMV* cytomegalovirus, *EBV* Epstein-Barr virus, *VZV* varicella zoster virus, *HIV* human immunodeficiency virus, *HCV* hepatitis C virus, *HBeAg* hepatitis B virus early antigen, *HBsAg* hepatitis B surface antigen, *HBsAb* hepatitis B surface antibody

28.2.1 Surgical Technique and Postoperative Care

The entire length of the small bowel from the ligament of Treitz to the ileocecal valve is measured. Subsequently, the cecum and the terminal ileum are identified and marked approximately 30 cm proximal from the ileocecal junction. The donor operation consists of harvesting 200 cm of distal ileum (160 cm for pediatric recipients), preserving at least 20–30 cm of terminal ileum and ileocecal valve to avoid macrocytic anemia and shortened transit time. The vascular pedicle of the graft is formed by the distal branches of the SMA and SMV or, alternately, by the ileocolic artery and vein, and they are anastomosed to the infrarenal aorta and cava of the recipient, respectively.

If the procedure involved a combined intestinal and liver transplant, the donor operation becomes more complex. Combined living donor intestinal and liver transplants have only been done for pediatric patients. If the recipient remains stable after the liver is implanted, the intestinal procurement (and consequently the transplant) can be performed; otherwise, the incision is closed and the intestinal transplant is rescheduled, preferably within the two first weeks after the liver transplant.

It is very important that the donors have adequate follow-up care. After discharge, they need to be evaluated on a monthly basis and then annually to review their eating and defecation patterns as well as any complications. The donor should also undergo vitamin B12 assays at 1, 6, and 12 months postdonation to ensure adequate vitamin B12 absorption.

Benedetti et al. report a case of chronic diarrhea among the donors, but it was resolved with medical therapy consisting of Imodium and cholestyramine [11]. For 11 donors, out of their total cohort of LD intestinal transplants at the University of Illinois Hospital, the authors also reported a 36.4 % reduction in LDL and a 22.3 % decrease in total cholesterol levels when compared with their respective predonation lipid profiles, and they noted the difference was statistically significant [12]. However, a further follow-up in a greater cohort should be completed to conclude this finding.

Although the number of LD intestinal transplants is relatively small, there have been no reports of donor mortality or life-threatening complications [13]. Nevertheless, a more extensive follow-up is necessary to determine the presence of postsurgical complications, such as intestinal adhesions.

28.3 Recipient

Registry data suggest that the patient and graft survival rates are similar for both LD and DD intestinal transplants. Nevertheless, using a living donor can reduce the mortality rate for those on the waiting list, which is especially high for candidates for combined liver/bowel transplant less than 5 years of age (www.unos.org, SRTR & OPTN Annual Data Report, 2012).

About 15 % of patients receiving TPN for more than 1 year develop end-stage liver disease. In children, the incidence of liver disease is higher, especially in patients with less than 30–40 cm of remnant bowel [14]. Liver disease remains the

leading indication for performing intestinal transplantation in children, followed by loss of central venous access to provide parenteral nutrition.

The indications for intestinal transplantation in pediatric patients were updated in 2010 by Avitzur and Grant [15] (Table 28.2).

A multidisciplinary evaluation of the patient with intestinal failure is essential to assess adequate candidacy for transplantation and to ensure best outcomes. The evaluation process must elucidate the following: (1) the failure to wean of TPN after application of other surgical strategies for intestinal rehabilitation, besides transplantation; (2) the need of intestine or combined liver/intestine transplantation; (3) the state of the remnant intestine and the patency of the great vessels; (4) and the absence of absolute contraindications or associated disease that can put the patient at risk during the procedure or postoperative period. All the aspects of the recipient evaluation are summarized in Table 28.3.

Although the criteria used for listing deceased and living donor candidates are the same, we believe that certain patients may have a greater benefit from the living donor option. Adults with an identical twin or HLA-identical sibling as a donor candidate should be transplanted without delay. In our experience, using donors with at least one haplotype match has been extremely favorable, with no acute rejection episodes during the first year posttransplant. Highly sensitized patients may benefit from desensitization protocols, easily performed in the contest of a living donor bowel transplant in analogy to similar plasmapheresis-based strategies in living donor kidney transplantation. In children affected by ultra-short bowel syndrome with slim possibilities of successful weaning of TPN, LD intestinal transplant should be considered early in order to avoid progression to end-stage liver disease. For children who present TPN-related cirrhosis, the option of combined liver/bowel transplant from an adult living donor may contribute to minimize the probability of death on the waiting list, which is extremely high in this patient population.

28.3.1 Surgical Technique and Postoperative Care

A midline incision is made. After the remaining small bowel is mobilized, the infrarenal aorta artery and vena cava are identified and dissected free from the takeoff of

Table 28.2 Indication for pediatric intestinal transplantation

Indication for intestinal transplantation in pediatric patients
Loss of 50 % of available central venous accesses due to thrombosis
Recurrent septic episodes, resulting in multiorgan failure, shock, and metastatic infectious loci (more than two episodes per year)
Imminent or overt end-stage liver disease
Ultra-short bowel syndrome
High risk of death attributable to the underlying disease
Frequent hospitalization
Severe dehydration episodes
Lack of family support or unwillingness to accept long-term TPN

Table 28.3 Recipient evaluation

Flowchart for recipient evaluation
Comprehensive analysis of medical and surgical history, review of systems, physical examination, current medications, current nutrition requirements
Blood group, HLAa type, panel of reactive antibody
Upper and lower gastrointestinal barium study, esophagogastroduodenoscopy and colonoscopy, CT scan abdomen and pelvis, motility studies (if indicated)
Height, weight, anthropometric measurements, nutritional support, comprehensive metabolic panel, zinc
Prothrombin time, partial thromboplastin time, alpha-fetoprotein, ammonia. Doppler ultrasound of liver and liver biopsy (if indicated)
Electrocardiogram, chest X-ray, echocardiogram, stress test if more than 50 years of age or with cardiac history, and risk factors (hypertension, diabetes mellitus)
Abdominal ultrasound with size of kidneys, triple renal scan, 24 h creatinine clearance
Doppler ultrasound of upper and lower extremities veins
History of infection episodes, immunization, serology (CMV, EBV, VZV, HIV, HCV, HBeAg, HBsAg, HBsAbb, measles, rubella, and mumps titers), complete blood count. Blood, urine, and stool culture
Anesthesia history, surgical procedures, and drug allergies
Child life and development
Psychiatry evaluation, social work consultation
Doppler ultrasound of great vessels and angiography or MRI or 3D-angio-CT scan (if indicated)

Source: Data from Ref. [15]
aHLA histocompatibility leukocyte antigen, *bCMV* cytomegalovirus, *EBV* Epstein-Barr virus, *VZV* varicella zoster virus, *HIV* human immunodeficiency virus, *HCV* hepatitis C virus, *HBeAg* hepatitis B virus early antigen, *HBsAg* hepatitis B surface antigen, *HBsAb* hepatitis B surface antibody

the renal vessels to the level of their bifurcations. The arterial anastomosis is done first, since it is more technically challenging due to the small diameter of donor's artery the arteriotomy is made somewhere at the level between the origin of the renal arteries and inferior mesenteric artery. Given the small size of the ileocolic artery from the donor, the end-to-side ileocolic artery-to-infrarenal aorta anastomosis is constructed in an interrupted fashion. Continuing with the vein anastomosis, an appropriate site on cava is chosen for the venotomy, usually 2–3 cm proximal to the arterial anastomosis. The venous anastomosis is done with the quadrangulation technique, and the end-to-side ileocolic vein to infrarenal cava anastomosis is completed by continuous corner sutures. When the proximal end of the intestinal graft is identified, the anastomosis to the remaining recipient duodenum/jejunum could be made in an end-to-end, end-to-side, or side-to-side fashion. Our preference is to perform a handsewn, two-layer side-to-side anastomosis to the remaining recipient duodenum/jejunum. The handsewn technique decreases the risk of intraluminal anastomotic bleeding, as compared to stapled anastomosis.

The distal end of the donor graft should be brought out as a stoma to allow an easy access for endoscopy and biopsy. Exception could be made when the donor is

identical tween. The first 24–48h are critical due to surgical trauma, the degree of ischemia and reperfusion injury, and onset of immunosuppression. Initially, vital signs, color of the ostomy, and laboratory parameters are monitored every 4 h. An important element to immediately monitor posttransplant is systemic anticoagulation: due to the small diameter of the ileocolic vessels of the LD, they are more prone to vascular thrombosis. On posttransplant day 7, a small bowel follow-through contrast study is performed to confirm intactness of the anastomosis, and on the next day, the first graft biopsy is to be executed. After an anastomotic leak is ruled out, recipients begin a clear liquid diet. For recipients of a combined LD liver and intestinal transplant, postoperative care is initially dictated by the liver graft function. Once liver function has stabilized, the attention can be directed to the intestinal graft function.

The immunosuppression and follow-up of LDIT recipient do not differ significantly from DD recipients.

28.4 Current Status of Intestine Transplantation

According to United Network for Organ Sharing (UNOS) data, the total number of registrations on the intestine waiting list in 2014 is 261, where 54.2 % of the candidates are under 18 years of age. The proportion of newly listed patients who were 18 years of age or older had been increasing in the prior decade. However, the number of patients on the waiting list under 18 years of age still remained higher as compared to patients older than 18 years of age. This is particularly true for patients under 5 years of age (71.4 % and 51.8 %, respectively) (www.unos.org 2014). This data further indicates that pediatric patients have a higher risk of life-threatening complications secondary to TPN, when compared with adults.

During the last decade, the number of intestinal transplants increased more than twofold. In 2009, there was a total of 180 intestinal transplants, of which 94 (52 %) were for recipients less than eighteen (18) years of age. This increase was due primarily to a higher number of isolated intestine transplants as well as to increased number of combined liver/intestine transplants. Through the same year 89 (49.4 %), recipients required a combined liver and intestinal transplant (www.unos.org, SRTR & OPTN Annual Data Report, 2012). Children are the primary candidates for intestinal transplantation, and more than 70 % are affected by intestinal and liver failure. Recipients of a combined graft experience better graft survival outcomes compared to those who received an isolated intestinal transplant [16, 17].

According to UNOS, between 1990 and 2013, the rate of DD intestinal transplants had increased from 0.2 % to 4.3 %. However, the rate of LD intestinal transplants remains very low, with only one transplant performed in 2013. The total number of LD intestinal transplants in the USA is 40, 26 of which are performed by the team at The University of Illinois at Chicago. Our longest living donor intestinal graft survival is 15 years (unpublished data). Current data indicates that the 5-year patient survival probability was superior for LD intestinal transplant recipients as compared to intestinal/liver and deceased intestinal transplant recipients (2011 Intestinal Transplant Registry Report, www.intestinetransplant.org). However, the

experience with LD intestinal transplants remains limited, with a very small number of procedures been performed worldwide.

In conclusion, the technical details of the LD intestinal transplantation had been perfected, leading to results comparable with those of the deceased donor intestinal transplantation. However, LD intestinal transplantation should be limited in accordance with specific indications. In particular, the best indication for combined LD liver/intestinal transplantation would be a pediatric recipients with intestinal and hepatic failure. For these potential recipients, the virtual elimination of waiting time may diminish the high mortality on the waiting list. Isolated LD intestinal transplantation may further be indicated for candidates in need of an intestinal transplant with lack of central venous access as a rapid rescue strategy. Potentially, LD intestinal transplantation could be used with highly sensitized recipients, to allow the application of desensitization protocols. Finally, in the specific case of available identical twins or HLA-identical sibling, LD intestinal transplantation has a significant immunological advantage and should be offered.

References

1. Current world literature. Small bowel transplantation. Curr Opin Organ Transplant 2013;18:379–82.
2. Alican F, Hardy JD, Cayirli M, Varner JE, Moynihan PC, Turner MD, Anas P. Intestinal transplantation: laboratory experience and report of a clinical case. Am J Surg. 1971;121:150–9.
3. Deltz E, Mengel W, Hamelmann H. Small bowel transplantation: report of a clinical case. Prog Pediatr Surg. 1990;25:90–6.
4. Deltz E, Schroeder P, Gebhardt H, Gundlach M, Engemann R, Timmermann W. First successful clinical small intestine transplantation. Tactics and surgical technic. Chirurg. 1989;60:235–9.
5. Benedetti E, Pirenne J, Chul SM, Fryer J, Fasola C, Hakim NS, Troppmann C, Beebe DS, Carr RJ, Belani KG, et al. Simultaneous en bloc transplantation of liver, small bowel and large bowel in pigs – technical aspects. Transplant Proc. 1995;27:341–3.
6. Gruessner RW, Sharp HL. Living-related intestinal transplantation: first report of a standardized surgical technique. Transplantation. 1997;64:1605–7.
7. Morris JA, Johnson DL, Rimmer JA, Kuo PC, Alfrey EJ, Bastidas JA, Dafoe DC. Identical-twin small-bowel transplant for desmoid tumour. Lancet. 1995;345:1577–8.
8. Fujimoto Y, Koshiba T, Ogura Y, Uryuhara K, Kasahara M, Kaibori M, Egawa H, Uemoto S, Inomata Y, Tanaka K. Living-related donor small bowel transplantation: first case in Japan. Transplant Proc. 1998;30:3441–2.
9. Lee MD, Kim DG, Ahn ST, Moon IS, Choi MG, Hong SG, Park SC, Chung IS, Choi JY, Yoon SK, Kim SI, Choi JH, Jung ES. Isolated small bowel transplantation from a living-related donor at the catholic university of Korea – a case report of rejection -free course. Yonsei Med J. 2004;45:1198–202.
10. Ishii T, Wada M, Nishi K, Sato T, Amae S, Yoshida S, Nakamura M, Satomi S, Kato T, Hayashi Y. Two cases of living-related intestinal transplantation. Transplant Proc. 2006;38:1687–8.
11. Ghafari JL, Bhati C, John E, Tzvetanov IG, Testa G, Jeon H, Oberholzer J, Benedetti E. Long-term follow-up in adult living donors for combined liver/bowel transplant in pediatric recipients: a single center experience. Pediatr Transplant. 2011;15:425–9.
12. Ghafari J, Tzvetanov I, Spaggiari M, Jeon H, Oberholzer J, Benedetti E. The effect of small bowel living donation on donor lipid profile. Transpl Int. 2012;25:e19–20.

13. Gruessner RWG, Benedetti E. Living donor organ transplantation. New York: McGraw Hill Professional, McGraw-Hill Medical; 2008. p. 1. online resource.
14. Kelly DA. Liver complications of pediatric parenteral nutrition – epidemiology. Nutrition. 1998;14:153–7.
15. Avitzur Y, Grant D. Intestine transplantation in children: update 2010. Pediatr Clin North Am. 2010;57:415–31, table of contents.
16. Gangemi A, Tzvetanov IG, Beatty E, Oberholzer J, Testa G, Sankary HN, Kaplan B, Benedetti E. Lessons learned in pediatric small bowel and liver transplantation from living-related donors. Transplantation. 2009;87:1027–30.
17. Testa G, Holterman M, Abcarian H, Iqbal R, Benedetti E. Simultaneous or sequential combined living donor-intestine transplantation in children. Transplantation. 2008;85:713–7.

Small Bowel Transplantation

29

Antonia D'Errico, Francesco Vasuri, and Alberto Bagni

Abbreviations

ACR	Acute cellular rejection
AMR	Antibody-mediated rejection
CMV	Cytomegalovirus
CR	Chronic rejection
DSA	Donor-specific antibody
EBV	Epstein-Barr virus
GVHD	Graft-versus-host disease
IITx	Isolated intestinal transplantation
MTVx	Multivisceral transplantation
PTLD	Post-transplant lymphoproliferative disease

In the last 15 years, intestinal transplantation has become a viable alternative to parenteral feeding in the management of irreversible gastrointestinal failure in children and adults [1–3]. The graft may consist in the small bowel (isolated intestinal transplant, IITx) or also include liver, colon, pancreas, and stomach (multivisceral transplant, MVTx). MVTx has improved graft and patient survival so that it is comparable to and in some studies better than IITx [4].

Small bowel transplantation presents many challenges due to the high incidence of ACR and CR, bacterial and viral infections and the frequently poor general conditions of the recipients. The post-operative management is difficult and represents a delicate balance between heavy immunosuppressive treatment and the increased risk

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of infections, PTLD especially in paediatric patients and raising the graft immune response to the host (GVHD). Heavy immunosuppressive therapy can itself lead to damage in other organs and tissues, particularly the kidney [5, 6].

In addition to the clinical impression and endoscopic examination, histology represents one the most accurate diagnostic tools. Therefore, graft biopsies are often necessary in cases of graft impairment to establish a diagnosis among different possibilities (AR, infections, PTLD, etc.).

29.1 Pathology of Intestinal Allograft Diseases

Methods: The technical procedure is simple. Biopsy specimens from the graft mucosa are fixed in formalin and subsequently paraffin embedded by standard techniques. Consecutive sections are cut to obtain several slides. Standard staining (haematoxylin-eosin) is performed on some slides, and the remaining unstained slides are available in case immunohistochemical or histochemical stainings become necessary. A biopsy should be frozen and preserved in a deep freezer at −80 °C for immunohistochemistry or DNA/RNA extraction.

It is recommended that samples from native bowel mucosa be evaluated for any inflammatory infiltrate or other morphological features mimicking acute rejection.

29.1.1 Alloimmune Disease in IITx and MVTx

29.1.1.1 Acute Cellular Rejection

ACR represents an immune-mediated injury against transplanted small intestine: mononuclear inflammatory infiltrate and crypt injury are the main morphological changes. During the first weeks post-transplant, the donor graft is progressively replaced by recipient lymphoid tissue. Despite adequate immunosuppression, the infiltrated areas become sites of intense immune stimulation, and the inflammatory infiltrate begins to extend into the lamina propria resulting in epithelial damage and crypt cell apoptosis. ACR is the main cause of intestinal graft loss in the first 2 months after transplant [7]. The diagnosis of ACR includes clinical symptoms, endoscopic findings and histologic features. The usual symptoms are fever, abdominal pain, increased stoma output, watery diarrhoea, nausea and vomiting. At endoscopy, the mucosa shows different degrees of damage ranging from distortion of mucosal pattern, oedema and hyperaemia to ulceration, extensive denudation and loss of peristalsis.

At least two or three biopsies should be performed both in the damaged mucosa and in the native segments. The anastomotic mucosa is better avoided as it might be confounding for the pathologist.

A unified grading scheme for ACR in small bowel allograft was proposed at the Pathology Workshop of the VIIIth International Small Bowel Transplant Symposium (September 10, 2003), Miami, FL, USA [8].

No Evidence of Acute Rejection: Grade 0/Score 0

The tissue from the bowel allograft is very similar to normal native bowel. If the bowel shows pathological changes, they are clearly different from those associated with acute cellular rejection.

Indeterminate for Acute Rejection: Grade Ind/Score 1

The crypts show minor epithelial cell injury. Epithelial cell apoptosis is present but with less than six apoptotic bodies per ten crypt cross sections (Fig. 29.1). The damage is mild and focal, with isolated superficial epithelial injury along the surface not being characteristic of this grade (other entities should be entertained); the overlying mucosa is intact. The mild inflammatory infiltrate is mononuclear including blastic or activated lymphocytes (Fig. 29.2). There is no evidence of non-specific enteritis.

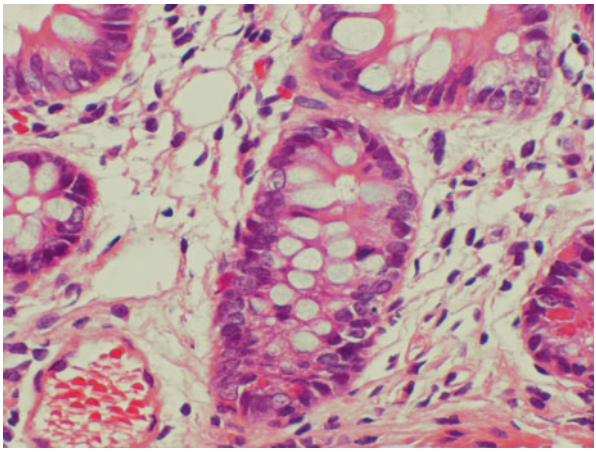

Fig. 29.1 An isolated apoptotic body in a crypt. Less than six apoptotic bodies per ten crypt cross sections are seen in cases graded as indeterminate for acute rejection (H&E 20×)

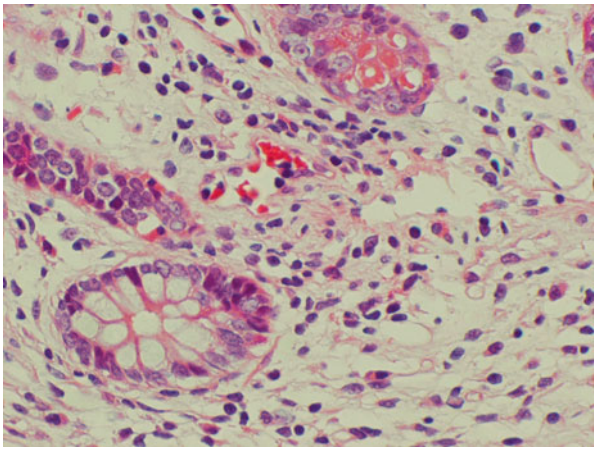

Fig. 29.2 Indeterminate for acute rejection. A mild mononuclear inflammatory infiltrate including blastic or activated lymphocytes is present (H&E 20×)

Acute Cellular Rejection, Mild: Grade 1/Score 2

Crypt injury is more evident. There are six or more epithelial apoptotic bodies per ten crypt cross sections together with other features correlated with mucosal damage such as mucin depletion, cytoplasmic basophilia, decreased cell height, nuclear enlargement and hyperchromasia and increased mitotic activity (Fig. 29.3). The villi demonstrate blunting and architectural distortion. The epithelial cell changes tend to be diffuse. The inflammatory infiltrate is mild to moderate with lymphocytes, including blastic or activated cells, eosinophils and occasional neutrophils. Oedema and vascular congestion are often present.

Acute Cellular Rejection, Moderate: Grade 2/Score 3

Again six or more apoptotic bodies per ten crypt cross sections are present. In addition, single crypts may contain multiple apoptotic bodies with foci of "confluent apoptosis" causing erosions in crypt epithelium and focal crypt loss (Fig. 29.4). The inflammatory infiltrate (mononuclear cells with blasts and activated lymphocytes) is moderate to severe. Sometimes the superficial mucosa shows focal erosions, but this is not a prerequisite for the diagnosis.

Acute Cellular Rejection, Severe: Grade 3/Score 4

Crypt damage and destruction are prominent with crypt loss. Diffuse mucosal erosion and/or ulceration are present. Sometimes biopsy specimens show only granulation tissue and/or a pseudomembranous component (Fig. 29.5a, b). The number of epithelial apoptotic bodies varies and is not correlated to the severity of crypt loss: epithelial cell loss is frequently complete at the time of biopsy. When some epithelium is left adjacent to the ulceration, it usually exhibits rejection-associated changes, such as crypt epithelial damage [8].

Apoptosis is characteristic of acute rejection although several inflammatory and immunologic processes (i.e. viral and autoimmune enteritis, GVHD) can be associated with an increase in apoptotic bodies. Investigation of both graft tissue and native mucosa can help pathologists and clinicians establish a correct diagnosis [9].

Top differential diagnoses:

- Reperfusion injury (Fig. 29.6)
  - Oedema of the villi
  - Surface denudation
  - Ischaemic injury with epithelial regeneration
  - Fewer apoptotic bodies
- Viral infections [10–14]
  (a) Cytomegalovirus (CMV)
    - Nuclear inclusions with owl's eye morphology (Fig. 29.7a)
    - Neutrophils in the lamina propria along the luminal epithelial surface and in the crypts
    - Fewer apoptotic bodies
    - CMV immunohistochemistry (Fig. 29.7b)

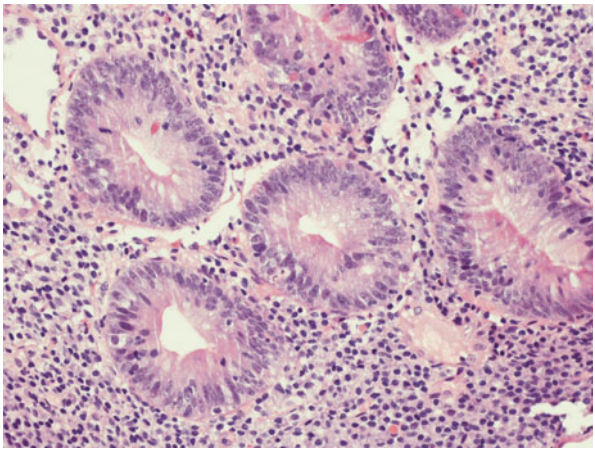

Fig. 29.3 In this biopsy, graded as acute cellular rejection, mild, here are shown crypt injuries: mucin depletion, cytoplasmic basophilia, decreased cell height, nuclear enlargement and hyperchromasia (H&E 20×)

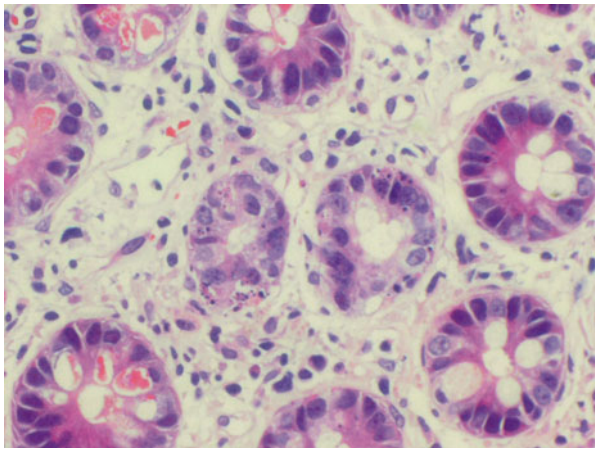

Fig. 29.4 Moderate acute cellular rejection. Single crypts may contain multiple apoptotic bodies with foci of "confluent apoptosis" causing erosions in crypt epithelium and focal crypt loss (H&E 20×)

(b) Epstein-Barr virus (EBV)
- Lymphocytic infiltrate in both the mucosa and epithelium (surface and crypts) (Fig. 29.8)
- No evidence of apoptotic bodies
- Lymphoid nodules extended to crypts, high risk of PTLD

(c) Adenovirus
- Surface epithelial degenerative changes
- Characteristic inclusions most commonly in surface epithelium (round to crescent-shaped, "smudge" cells, eosinophilic inclusions)
- Apoptotic bodies

(d) Rotavirus
- Mild to moderate villous blunting
- Mixed inflammatory infiltrate (lymphocytes, plasma cells, eosinophils and neutrophil)
- No significant increase in crypt apoptosis

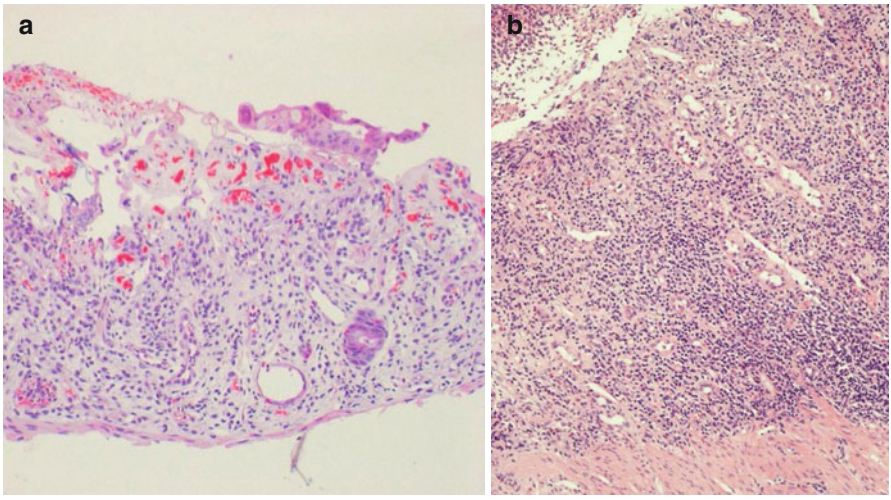

Fig. 29.5 (**a, b**). Severe acute cellular rejection. Crypt damage and destruction are prominent with crypt loss. Sometimes biopsy specimens show only granulation tissue and/or a pseudomembranous component (H&E 10×)

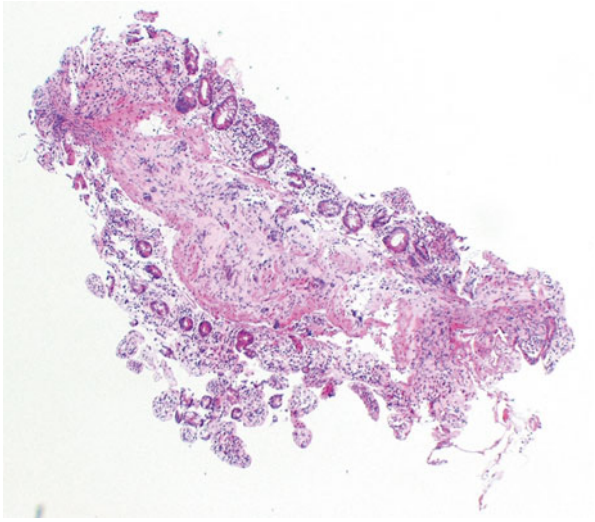

Fig. 29.6 Ischaemia-reperfusion injury. Mucosa shows blunting and denudation of the villi with a variable inflammatory infiltrate and oedema (H&E 5×)

29.1.1.2 Antibody-Mediated Rejection

ITx and MVTx can exhibit two types of AMR:

- Hyperacute and accelerated acute rejection
- Acute antibody-mediated rejection

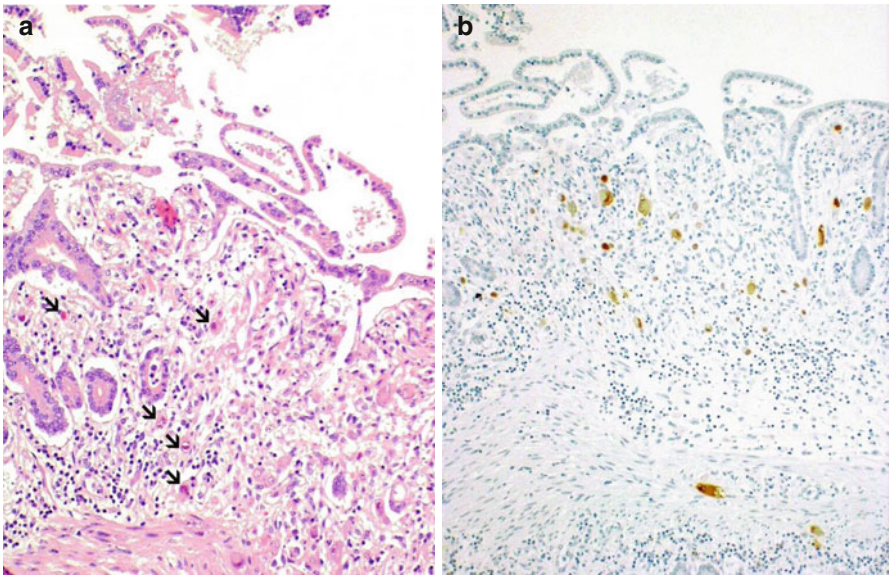

Fig. 29.7 (**a, b**) CMV infection. Nuclear inclusions in stromal cells in the mucosa (*arrows*, **a** H&E 10×) are immunoreactive for CMV antibody (**b** IHC staining 10×)

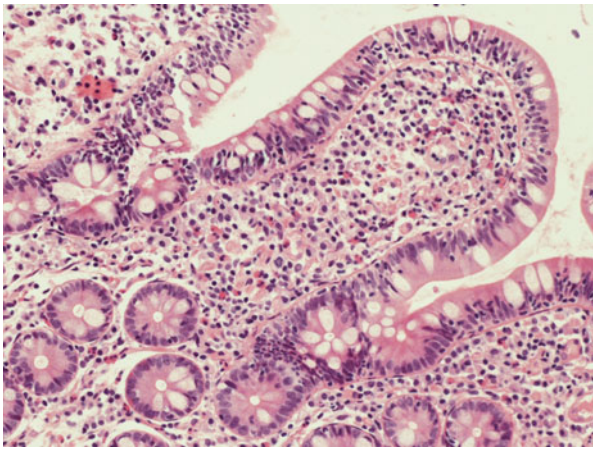

Fig. 29.8 EBV infection. Intraepithelial lymphocytic infiltrate in EBV positive patient (H&E 10×)

Hyperacute and Accelerated Acute Rejection

This severe disease is the result of preformed donor-specific antibody (DSA) due to a previous allosensitization (pregnancy, blood transfusion or prior allogenic tissue exposure). The greater the allosensitization is, the more severe the clinical and pathological progression of the disease. The allograft organ can be rejected within minutes to hours (hyperacute rejection) or a few days (accelerated acute rejection) after transplantation [6, 15]. Cross-match tests in gastrointestinal transplantation have markedly reduced the incidence of these complications. The antibody response is directed at the endothelium of the donor microvasculature activating complement, innate immune response and the coagulation cascade [16]. The main morphological alterations are the result of a severe antibody-mediated response to the endothelia:

- Dilated capillaries with prominent endothelial cells and neutrophils
- Marked congestion
- Capillary fibrin thrombi
- Occasional mucosal ulceration
- C4d staining in the endothelium of mucosal and submucosal capillaries

The resected specimens usually display arterial thrombosis and vasculitis [16].

Acute Antibody-Mediated (Humoral) Rejection (AMR)

The diagnosis of AMR is difficult and requires specific morphological and histochemical features and the knowledge of whether pre- and/or post-transplant alloantibodies are present. AMR can be isolated or associated with a T-cell-mediated acute rejection. The absence of previous allosensitization is a good prognostic factor, but allospecific HLA antibodies may arise de novo after transplantation and can trigger the onset of AMR [17].

The mucosa shows mild vascular congestion of the capillaries with red cell extravasation. These changes are not specific, being shared with other pathologies like bacterial and viral enteritis and ischaemia. In some cases, immunological endothelial damage can occur in the mesenteric arteries inducing progressive mucosal ischaemic damage and fibrosis. Vasculitis of the mesenteric arteries can lead to sclerosing mesenteritis; only surgical specimens can reveal these morphological changes [16].

Top differential diagnoses:

- ACR (the two conditions can coexist)
- Reperfusion injury
- Surgical complications
- Enteritis

29.1.1.3 Chronic Rejection

As with other solid organ transplants, CR is a progressive and chronic graft disease characterized by obliterative arteriopathy and graft loss. CR is insidious and lacks any morphological hallmarks in the mucosa. Clinical symptoms (watery diarrhoea, protein loss) are common to other diseases, but they are progressive and

unresponsive to therapy. Submucosa and mesenteric obliterative arteriopathy is the main morphological change but is evident only in the surgical specimen of the failed graft or in full-thickness biopsy.

At endoscopy, the villi are flat and irregular, and ulcerative areas can be evident, while the bowel can be firm and fibrotic.

Mucosal biopsies show different degrees of fibrosis, low-grade apoptosis, crypt separation, mucin depletion and ischaemic damage. Not all these changes are diagnostic of CR, and clinical correlations are always required.

Surgical specimens often present serosal adhesion of adjacent bowel tracts and mesenteritis with firm, solid adipose tissue embracing the graft (Figs. 29.9 and 29.10). The wall is firm and thickened.

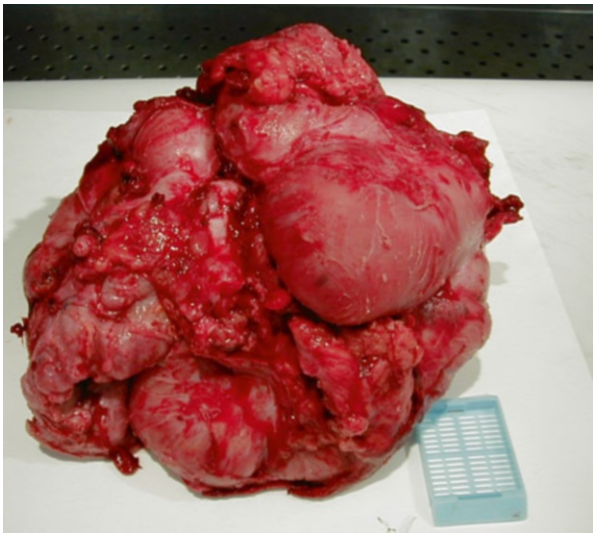

Fig. 29.9 Chronic rejection. Intestinal graft removed. Diffuse peritoneal fibrosis

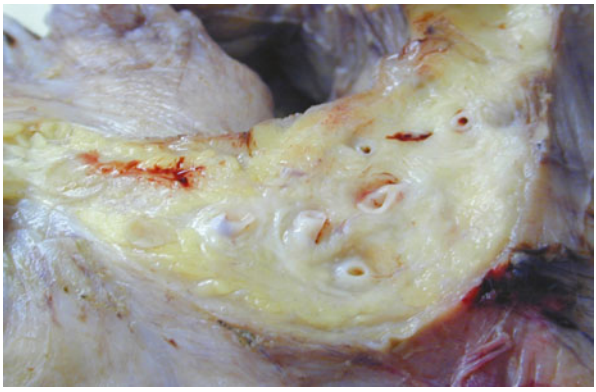

Fig. 29.10 Chronic rejection. Intestinal graft removed. Perivascular fibrosis and mesenteritis in the adipose tissue

At histology the hallmark of CR is obliterative arteriopathy. Marked intimal hyperplasia, foam cells and a mild mononuclear inflammatory infiltrate are the main changes occurring in the medium-sized arteries in the submucosa and mesentery and mucosal ulcers (Figs. 29.11 and 29.12) [3, 6, 9].

Top differential diagnoses:

- Severe ACR
- CMV chronic infection
- Vascular diseases

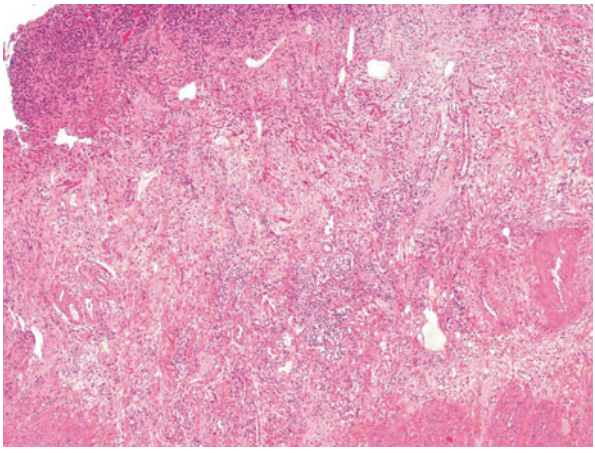

Fig. 29.11 Chronic rejection. Submucosal arteries with thickened wall and narrowed lumen, vasculitis and ulcerated mucosa (H&E 5×)

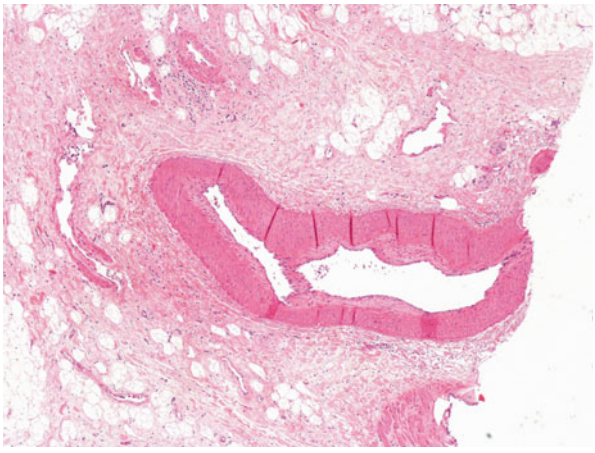

Fig. 29.12 Chronic rejection. Perivascular fibrosis and intimal thickening at histology (H&E 10×)

29.1.2 Rejection in Other Organs in MVTx

In MVTx the different allografts can display varying forms and degrees of rejection. The first site to be involved is usually the distal part of the ileum, but the duodenum, stomach and colon may also be affected. Unlike the liver graft, MVTx seldom leads to rejection [19]. In addition, the criteria for the diagnosis of ACR and CR have to take into account organ-specific alterations.

29.1.2.1 Stomach Rejection

Stomach transplantation may be a part of a MVTx. The ACR changes in the grafted stomach are very similar to those encountered in small bowel allograft rejection [18].

The grading scheme proposed by Garcia et al. in 2004 suggests evaluating morphological changes in the different components of the mucosa: surface epithelium, lamina propria and glandular epithelium. The evaluation of apoptosis differs from bowel biopsies.

Morphological changes [19]:

- Epithelial apoptosis, expressed as the number of apoptotic bodies/10 HPF
- Inflammatory infiltrate: lymphocytes and plasma cells with some neutrophils and eosinophils
- Architectural disarray of the mucosa: erosions, ulcers, hyperplasia and atrophy
- Cellular changes (hyperplasia and nuclear pleomorphism)
- Oedema, congestion and haemorrhage

29.1.2.2 Colon Rejection

Colon transplantation is part of MVTx. Small bowel and colon share many morphological changes in ACR.

Morphological changes [18]:

- Crypt apoptosis is the hallmark feature.
- Inflammatory infiltrate lymphocytes (blasts and activated lymphocytes), plasma cells and neutrophils, graded as mild, moderate or severe.
- Granulation tissue.
- Fibrosis.
- Mucosal regeneration.

Graft-Versus-Host Disease

GVHD is a rare but often devastating and life-threatening complication after solid organ transplantation. GVHD occurs when donor alloreactive T lymphocytes transferred within the transplanted organ trigger a destructive cellular immune response against the recipient's tissue. Acute GVHD mainly involves skin, liver and gastrointestinal tract. Symptoms include a generalized maculopapular, erythematous rash

with palm and sole involvement, sometimes pruritic and painful, jaundice, vomiting, diarrhoea and respiratory distress [20]. The incidence of GVHD is between 5 % and 10 %, but the mortality is high both in paediatric and adult recipients [21]. Among 241 patients evaluated by Wu et al. after intestinal transplantation, 22 presented clinical signs suggestive of GVHD. They concluded that younger children, MVTx recipients and those with splenectomy are at higher risk of developing GVHD [22].

Main pathological features:

- Skin: spongiotic dermatitis with lymphocytic exocytosis, vacuolar degeneration and ulcers [18, 23] (Fig. 29.13).
- Liver: progressive damage to the duct cells by lymphocytes and progressive loss of ducts.
- Native gastrointestinal tract: apoptosis of the glands/crypts is the hallmark; mixed inflammatory infiltrate, ulcers and granulation tissue [18].

29.1.3 Non-alloimmune Disease in ITx and MVTx

29.1.3.1 Ischaemia-Reperfusion Injury

Some changes due to organ preservation may occur in the mucosa in the first few days following transplantation (Fig. 29.6). The intestinal mucosa is highly sensitive to hypoperfusion and ischaemia, inducing various degrees of epithelial barrier dysfunction. Varying degrees of inflammation and capillary congestion may also be present. These changes resolve quickly and normal histology is usually restored within a week after transplantation [5, 9]. Ischaemia-reperfusion injury is known to

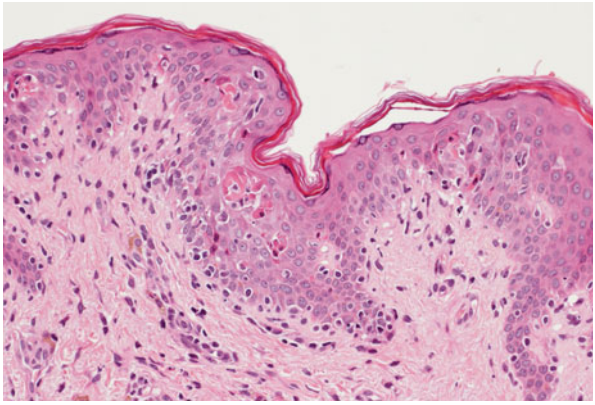

Fig. 29.13 GVHD. Lymphocytic infiltrate in upper dermis involving basal epidermal layer, vacuolar degeneration of epidermal basal cells, spongiosis and single or multiple necrotic keratinocytes (H&E 10×)

contribute to allograft rejection and carries a greater sensitivity to bacterial and viral infections [24, 25]. Polyethylene glycol (PEG) compounds added to transplant preservation solutions have been shown to attenuate damage from cold ischaemia both in experimental models and in human kidney transplantation [26, 27].

29.1.3.2 Infections

Immunosuppression in IITx and MVTx carries a higher risk of systemic and local infections in graft or native tissues. If a GI graft is involved, the symptoms (usually diarrhoea and fever) may simulate an acute rejection. In addition to microbiology and virology tests and cultures, biopsy is mandatory to identify the pathological process.

(a) Viral infections
Many viruses can involve intestinal recipients, including EBV, CMV, rotavirus, adenovirus, calicivirus (human calicivirus) and herpes simplex virus [2]. Recipients at highest risk for CMV or EBV diseases are those previously unexposed to the virus pretransplant (antibody negative) who receive an organ from an antibody-positive donor [28].
EBV infection
EBV is a B-lymphotropic herpesvirus 4 DNA virus. The spectrum of clinical disease includes a non-specific viral syndrome, mononucleosis and PTLD including EBV-associated malignant lymphoma (e.g. Burkitt's lymphoma). The main symptoms are increased stomal output, diarrhoea with fever, gastrointestinal bleeding and abdominal pain [29].

Histologic features [18]:

(A) *EBV enteritis*
- Inflammatory infiltrate: activated lymphocytes and plasma cells
- Increased intraepithelial lymphocytes
- Lymphoid aggregates in chronic infection
- These morphological changes can be detected both in the allograft and in native mucosa

(B) *PTLD*
- Small bowel allograft is the most common site.
- Mucosal changes can be patchy and scarcely representative.
- Perforation can be the first clinical sign.
- In some cases an intestinal mass can be detected.
- Lymph node involvement.
- Other organs can be involved.
- PTLD can be polymorphic or monomorphic. Biopsies should be evaluated by pathologists with long-standing experience both in transplant pathology and in lymph node proliferative disorders. All the specimens have to be tested in a first step for lymphocyte cell markers such as CD20, CD79 and CD3 and in situ hybridization for EBER, a marker of EBV-infected cells [18, 29].

(C) De novo *post-transplant smooth muscle tumour*
- The muscularis propria shows different changes during IITx and MVTx, both in the first steps (ischaemia and reperfusion) and in acute rejection [30].
- EBV-associated smooth muscle tumours are rare lesions occurring in immunocompromised patients [31].
- EBER stain shows diffuse nuclear staining of smooth muscle cells.
- The mucosa can be involved, but the diagnosis is currently performed on resected specimens.
- The main morphological feature is a proliferation of spindle cells with pale cytoplasm associated with marked vascular proliferation [18].

CMV infection
- Can occur any time post-transplant, more frequently after ACR.
- High risk of infection when the donor is seropositive and the recipient is seronegative.
- PCR monitoring and prophylactic treatment have reduced the morbidity and mortality.
  Histologic features: see the differential diagnosis with ACR.

Rotavirus and calicivirus infection
- Any time post-transplant.
- More frequent in children.
- Diarrhoea is the main symptom.
- At histology, blunt villi and a dense mononuclear infiltrate close to the luminal surface are characteristic features [9, 13, 32].

Adenovirus infection
- More commonly identified in children.
- Risk factors: younger age at transplant and aggressive immunosuppressive therapy.
- Histological changes involve both graft and native intestine [9].
  Histologic features: see the differential diagnosis with ACR.

(b) Bacterial and fungal infections [18, 33, 34]
- Most common bacterial agents: *Pseudomonas*, *Enterococcus*, *Escherichia coli*, *Staphylococcus*, *Klebsiella* and *Clostridium difficile*
- Most common fungal agents: *Aspergillus*, *Candida*, *Cryptococcus* and *Pneumocystis*

Symptoms are correlated to the site of infection and type of infective agent:
- Wound infection and dehiscence
- Fever and malaise
- Peritonitis
- Systemic involvement in some cases with multiorgan dysfunction

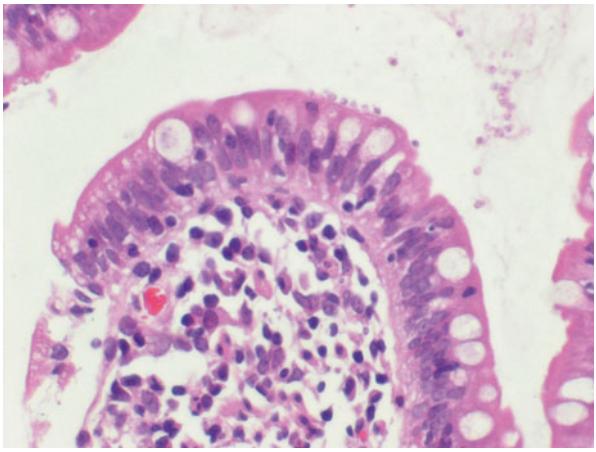

Fig. 29.14 Cryptosporidium parvum colitis. Basophilic dots on luminal border of epithelial cells (H&E 20×)

Histologic features:

Bacterial infections can induce villi blunting and swelling, increased mixed inflammatory infiltrate (lymphocytes, plasma cells and granulocytes) in the mucosa, erosions and ulcers. The presence of granulomas requires a search for acid-fast bacilli with histological staining and culture.

Clostridium Difficile infection induces a pseudomembranous enteritis/colitis.

Fungal agents are not identified in allograft intestinal biopsies. Many recipients with systemic fungal infections show pulmonary and central nervous system symptoms. In fatal cases autopsy is mandatory to evaluate the systemic infection and the aetiologic agent.

Cryptosporidium parvum, which is an HIV-related protozoan pathogen, causing frequent watery diarrhoea, nausea, vomiting, abdominal cramps and fever, has been found in small bowel transplant patients. The parasite may be seen on the luminal border of enterocytes in small bowel graft (Fig. 29.14).

References

1. Lacaille F. Intestinal transplantation: where are we? Where are we going? Curr Opin Organ Transplant. 2012;17:248–9.
2. Ruiz P. How can pathologists help to diagnose late complications in small bowel and multivisceral transplantation? Curr Opin Organ Transplant. 2012;17:273–4. Many reports suggest that MVTx plays a protective role against both acute cellular rejection (ACR) and chronic rejection (CR) compared with ITx, with a substantial decreasing of rejection disease.
3. Takahashi H, Kato T, Delacruz V, Nishida S, Selvaggi G, Weppler D, Island E, Moon JI, Levi DM, Tzakis AG, Ruiz P. Analysis of acute and chronic rejection in multiple organ allografts from retransplantation and autopsy cases of multivisceral transplantation. Transplantation. 2008;85:1610–6.
4. Tzakis AG, Kato T, Levi DM, Defaria W, Selvaggi G, Weppler D, Nishida S, Moon J, Madariaga JR, David AI, Gaynor JJ, Thompson J, Hernandez E, Martinez E, Cantwell GP, Augenstein JS, Gyamfi A, Pretto EA, Dowdy L, Tryphonopoulos P, Ruiz P. 100 multivisceral transplants at a single center. Ann Surg. 2005;242:480–90.

5. Lee RG, Nakamura K, Tsamandas AC, Abu-Elmagd K, Furukawa H, Huston WR, Reyes J, Tabasco-Minguillan JS, Todo S, Demetris AJ. Pathology of human intestinal transplantation. Gastroenterology. 1996;110:1820–34.
6. Ruiz P. Updates on acute and chronic rejection in small bowel and multivisceral allografts. Curr Opin Organ Transplant. 2014;19:293–302.
7. Vianna RM, Mangus RS. Present prospects and future perspectives of intestinal and multivisceral transplantation. Curr Opin Clin Nutr Metab Care. 2009;12:281–6.
8. Ruiz P, Bagni A, Brown R, Cortina G, Harpaz N, Magid MS, Reyes J. Histological criteria for the identification of acute cellular rejection in human small bowel allografts: results of the pathology workshop at the VIII international small bowel transplant symposium. Transplant Proc. 2004;36:335–7.
9. Remotti H, Subramanian S, Martinez M, Kato T, Magid MS. Small-bowel allograft biopsies in the management of small-intestinal and multivisceral transplant recipients. Arch Pathol Lab Med. 2012;136:761–71.
10. Florescu DF, Langnas AN, Grant W, Mercer DF, Botha J, Qiu F, Shafer L, Kalil AC. Incidence, risk factors, and outcomes associated with cytomegalovirus disease in small bowel transplant recipients. Pediatr Transplant. 2012;16:294–301.
11. de Mezerville MH, Tellier R, Richardson R,S, Hébert D, Doyle J, Allen U. Adenoviral infections in pediatric transplant recipients: a hospital-based study. Pediatr Infect Dis J. 2006;25(9):815–8.
12. Florescu DFF, Islam MK, Mercer DF, Grant W, Langnas AN, Freifeld AG, Sudan D, Basappa R, Dimaio D, Kalil AC. Adenovirus infections in pediatric small bowel transplant recipients. Transplantation. 2010;90:198–204.
13. Adeyi OA, Randhawa PA, Nalesnik MA, Ochoa ER, Abu-Elmagd M, Demetris AJ, Wu T. Posttransplant adenoviral enteropathy in patients with small bowel transplantation. Arch Pathol Lab Med. 2008;132:703–5.
14. Adeyi OA, Costa G, Abu-Elmagd KM, Wu T. Rotavirus infection in adult small intestine allografts: a clinicopathological study of a cohort of 23 Patients. Am J Transplant. 2010;10:2683–9.
15. Ruiz P, Carreno M, Weppler D, Gomez C, Island E, Selvaggi G, Nishida S, Moon J, Levi D, Tekin A, Tryphonopoulos P, Tzakis AG. Immediate antibody-mediated (hyperacute) rejection in small-bowel transplantation and relationship to cross-match status and donor-specific C4d-binding antibodies: case report. Transplant Proc. 2010;42:95–9.
16. Dick AAS, Horslen S. Antibody-mediated rejection after intestinal transplantation. Curr Opin Organ Transplant. 2012;17:250–7.
17. Abu-Elmagd KM, Wu G, Costa G, Lunz J, Martin L, Koritsy DA, Murase N, Irish W, Zeevi A. Preformed and de novo donor specific antibodies in visceral transplantation: long-term outcome with special reference to the liver. Am J Transplant. 2012;12:3047–60.
18. Chang A. Diagnostic pathology. Transplant Pathol. 2014;8:34–37. Amirsys eBook advantage. First Edition.
19. Garcia M, Delacruz V, Ortiz R, Bagni A, Wepler D, Kato T, Tzakis A, Ruiz P. Acute cellular rejection grading scheme for human gastric allografts. Hum Pathol. 2004;35:343–9.
20. Andres AM, Santamaría ML, Ramos E, Sarriá J, Molina M, Hernandez F, Encinas JL, Larrauri J, Prieto G, Trovar JA. Graft-vs-host disease after small bowel transplantation in children. J Pediatr Surg. 2010;45:330–6.
21. Shin CR, Nathan J, Alonso M, Yazigi N, Kocoshis S, Tiao G, Davies SM. Incidence of acute and chronic graft-versus-host disease and donor T-cell chimerism after small bowel or combined organ transplantation. J Pediatr Surg. 2011;46:1732–8.
22. Wu G, Selvaggi G, Nishida S, Moon J, Island E, Ruiz P, Tzakis AG. Graft-versus-host disease after intestinal and multivisceral transplantation. Transplantation. 2011;91:219–24.
23. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, Thomas ED. Review 1994 consensus conference on acute GVHD grading. Bone Marrow Transplant. 1995;15:825.

24. Siniscalchi A, Cucchetti A, Miklosova A, Lauro A, Zanoni A, Spedicato S, Berardi E, Aurini L, Pinna AD, Faenza S. Post-reperfusion syndrome during isolated intestinal transplantation: outcome and predictors. Clin Transplant. 2012;26:454–60.
25. Lenaerts K, Ceulemans LJ, Hundscheid IHR, Grootjans J, Dejong CHC, Olde Damik SWM. New insight in intestinal ischemia-reperfusion injury: implications for intestinal transplantation. Curr Opin Organ Transplant. 2013;18:298–303.
26. Valuckaite V, Seal J, Zaborina O, Tretiakova M, Testa G, Alverdy JC. High molecular weight polyethylene glycol (PEG-15-29) maintains mucosal microbial barrier function during intestinal graft preservation. J Surg Res. 2013;183:869–75.
27. Tsoulfas G, Agorastou P. Ischemia reperfusion injury and the immune system. J Surg Res. 2014;186:114–5.
28. Verghese PS, Schmeling DO, Knight JA, Matas AJ, Balfour HH. The impact of donor viral replication at transplant on recipient infections posttransplant: a prospective study. Transplantation. 2014;00:00Y00.
29. Green M, Michaels MG. Epstein–Barr virus infection and posttransplant lymphoproliferative disorder. Am J Transplant. 2013;13:41–54.
30. Schaefer N, Tahara K, Websky MV, Koscielny A, Pantelis D, Kalff JC, Abu-Elmagd K, Hirner A, Turler A. Acute rejection and the muscularis propria after intestinal transplantation: the alloresponse, inflammation, and smooth muscle function. Transplantation. 2008;85:1465–75.
31. Deyrup AT, Lee VK, Hill CE, Cheuk W, Toh HC, Kesavan S, Ein'en Chan E, Weiss SW. Epstein-Barr virus-associated smooth muscle tumors are distinctive mesenchymal tumors reflecting multiple infection events. A clinicopathologic and molecular analysis of 29 tumors from 19 patients. Am J Surg Pathol. 2006;30:75–82.
32. Eisengart LJ, Chou PM, Iyer K, Cohran V, Rajaram V. Rotavirus infection in small bowel transplant: a histologic comparison with acute cellular rejection. Pediatr Dev Pathol. 2009;2:85–8.
33. Primeggia J, Matsumoto CS, Fishbein TM, Karacki PS, Fredette TM, Timpone JG. Infection among adult small bowel and multivisceral recipients in the 30-day postoperative period. Transpl Infect Dis. 2013;15:441–8.
34. Florescu DF, Qiu F, Mercer DF, Langnas AN, Shafer LR, Kalil AC. Risk factors for systemic Candida infections in pediatric small bowel transplant recipients. Pediatr Infect Dis. 2012;31:120–3.

Part V

Combined Abdominal Transplantation

Combined Abdominal Transplantation: Liver–Kidney

30

Massimo Del Gaudio, Giorgio Ercolani, Matteo Cescon, Matteo Ravaioli, Chiara Zanfi, Valentina Bertuzzo, and Antonio Daniele Pinna

30.1 Indication

Improvement in posttransplant management, particularly in immunosuppressive therapy, has led to a dramatic increase in patient survival following solid organ transplantation. Specifically, immunosuppressive therapy with the calcineurin inhibitors (CNIs) cyclosporine and tacrolimus has enhanced survival after orthotopic liver transplantation (OLTX) [1, 2]. Despite their associated improved survival, CNIs are inherently nephrotoxic and often cited as the main cause of chronic renal failure (CRF) following OLTX [3–7]. In the first 6 months following OLTX, CNIs have been associated with nearly a 30 % decline in glomerular filtration rate (GFR) [3]. Moreover, CNIs contribute to the development of CRF in approximately 18 % of OLTX patients after 13 years, including 9.5 % who progress to end-stage renal disease (ESRD) [3]. Because nephrotoxicity may lead to the discontinuation of CNIs, less effective immunosuppressive agents are used, which may result in more frequent liver and renal graft dysfunction. For these reasons, CNI toxicity and the acceleration of underlying liver and renal disease may necessitate subsequent liver and/or kidney retransplantation.

Since the implementation of the model for end-stage liver disease (MELD) by the United Network for Organ Sharing (UNOS) in 2002 as an objective allocation system, priority has shifted to end-stage liver disease (ESLD) patients with renal insufficiency. This shift in priority has led to a rapid albeit unintentional increase in the number of simultaneous liver–kidney transplants (SLKTs). Specifically, since 2001,

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not only did the number of SLKT increase by more than 300 % but the proportion of SLKT to the overall number of OLTX more than doubled from 2.38 % in 2001 to 5.5 % in 2006 [8]. Although significant renal impairment had previously been considered a contraindication for OLTX, SLKT has become a well-established therapeutic option for end-stage renal and liver disease since the first SLKT performed by Margreiter et al. in 1984 [9]. There is compelling evidence supporting the theory for an immunoprotective role assumed by the transplanted liver in preventing renal allograft rejection in SLKT from the same donor. SLKT recipients span the gamut from well-compensated cirrhotics with end-stage renal disease (ESRD) to severely decompensated chronic liver patients suffering acute kidney injury requiring continuous venovenous hemofiltration in the intensive care unit. At the first extreme, the indication for kidney transplantation is clear but the indication for liver transplantation is less obvious. The liver transplant is usually not urgent, but prevents hepatic decompensation after kidney transplantation. Moreover, the liver may also facilitate kidney transplantation by shortening waiting time. At the second extreme, the issues are exactly reversed. The kidney transplant is not urgent since dialysis can be maintained indefinitely. However, inclusion of the kidney for these critically ill patients may avert early posttransplant complications related to renal failure and reduce the risk of future ESRD. The increasing prevalence of acute and chronic renal dysfunction among liver transplant candidates coupled with the burgeoning kidney transplant waitlist has motivated physicians to define and standardize selection criteria for SLKT [10–12]. The model for end-stage liver disease (MELD) scoring system was implemented in 2002 and has been widely accepted as an objective scale of disease severity and accurate predictor of liver waitlist mortality [13, 14]. Prioritization of liver transplant candidates with renal dysfunction by the MELD system has resulted in a substantial increase in the number of simultaneous liver–kidney transplants. There are currently no standard criteria for the evaluation of patients with acute kidney injury (AKI) or chronic kidney disease (CKD) requiring liver transplantation (LT). The decision to perform SLKT is generally driven by concern over the likelihood of recovery of renal function and the associated increase in mortality in patients with non-recovery of renal function following liver transplantation alone (LTA). Because the persistence of preoperative renal dysfunction following LT has been associated with inferior patient survival [15–20] combined with the fact that kidney waitlist survival is comparatively worse for candidates with a previous LT [21, 22], transplant programs often follow center-specific decision-making oriented toward ensuring adequate posttransplant renal function while considering the appropriateness of SLKT. Currently there are several pitfalls in the existing guidelines that make it difficult to accurately distinguish candidates who will benefit from SLKT from those who will not. These include the definition and duration of AKI, glomerular filtration rate (GFR) determination, and the duration of dialysis. It is well known that in patients with cirrhosis, mild degrees of renal dysfunction may go undiagnosed. The proposed organ procurement and transplantation network (OPTN) policy for SLKT criteria has defined AKI based on a GFR $\leq$ 25 mL/min for a duration of $\geq$6 weeks determined by modified diet in renal disease (MDRD) or direct measurements, such as iothalamate. In liver transplant candidates with AKI, duration of

dialysis is the main criterion used to determine SLKT candidacy. However, no universally accepted guidelines exist regarding when dialysis should be initiated in patients with cirrhosis; it is largely a subjective decision with a wide spectrum of practice variations. In 2004, in response to the lack of a standard definition for AKI, the Acute Dialysis Quality Initiative (ADQI) Workgroup developed a consensus definition and classification for AKI, the RIFLE (risk, injury, failure, loss, end stage) criteria, which stratified acute renal dysfunction into grades of increasing severity of AKI based on changes in patients' serum creatinine (Scr) or urine output [23]. Subsequently it was recognized that even smaller increases in SCr (absolute increase in SCr $\geq$ 0.3 mg/dL) are associated with adverse outcome, and thus, the criteria were modified in 2007 to broaden the definition of AKI [24]. The RIFLE criteria have been validated in more than 500,000 patients with AKI, including critically ill patients with cirrhosis pre- and post-liver transplantation, and have been shown to predict clinical outcomes with a progressive increase in mortality with worsening RIFLE class [25–29]. The summit attendees considered the following criteria as an indication for SLKT in patients who were on the liver transplant waitlist: (A) candidates with persistent AKI for $\geq$ 4 weeks with one of the following: Stage 3 AKI as defined by modified RIFLE, i.e., a threefold increase in Scr from baseline, Scr $\geq$ 4.0 mg/dL with an acute increase of $\geq$ 0.5 mg/dL or on renal replacement therapy, and eGFR $\leq$ 35 mL/min (MDRD-6 equation) or GFR $\leq$ 25 mL/min (iothalamate clearance); (B) candidates with chronic kidney disease (CKD), as defined by the National Kidney Foundation [30], for 3 months with one of the following: eGFR $\leq$ 40 mL/min (MDRD-6 equation) or GFR $\leq$ 30 mL/min (iothalamate clearance), proteinuria $\geq$ 2 g a day, kidney biopsy showing > 30 % global glomerulosclerosis or > 30 % interstitial fibrosis, and metabolic disease.

The most frequent indications are virus- or alcohol-related liver cirrhosis, polycystic disease, genetic or metabolic disorders, and cholestatic disease.

30.2 Timing

The rationale for SLKT is easily justified in patients with ESLD in the setting of ESRD requiring chronic renal replacement therapy (RRT). However, the matter is more complicated in patients with ESLD who develop acute renal failure when the duration or potential reversibility of the renal failure is uncertain as is often the case in hepatorenal syndrome (HRS) type II. HRS is generally not considered an indication for SLKT due to the well-documented reversibility of the renal failure after OLTX [31, 32]. It has also been shown that kidneys transplanted from donors with HRS result in good renal function [33]. However, there is currently no consensus as to the duration of HRS or RRT after which renal dysfunction is not reversible. The lack of this consensus sets the stage for the debate between proceeding with upfront SLKT versus LTA with the potential need for sequential renal transplant. The advantages of SLKT appear to outweigh the disadvantages. One main advantage of SLKT is the enhanced outcomes compared to kidney after liver transplantation (KALT) and liver after kidney transplantation (LAKT) likely due to the apparent immunoprotection afforded to the kidney by the transplanted liver.

Secondly, a well-functioning kidney allows optimal dosing of necessary immunosuppressants. Lastly, several studies have confirmed the presence of immune complex-mediated glomerulonephropathy (GN) in HCV-positive patients undergoing OLTX even in the absence of clinical signs or symptoms [34–37]. In HCV recipients in particular, the underlying renal disease is surely exacerbated following OLTX, which would otherwise be preserved in SLKT. The use of SLKT is an effective and appropriate therapy in patients with ESLD with proven irreversible or chronic ESRD. Although the recent increase in SLKT performed each year effectively decreases the number of potential donor kidneys available to patients with ESRD awaiting kidney transplantation, SLKT in patients with ESLD and ESRD is justified due to the lower risk of graft loss in SLKT compared to liver transplantation alone (LTA) as well as superior recipient and graft survival compared to serial liver–kidney transplantation.

There is a paucity of data regarding the need for organ liver transplantation OLTX in ESRD patients with asymptomatic liver disease including Child's A cirrhosis. This issue is important because of the incidence of hepatitis C positive (HCV+) in dialysis patients of 10–40 %, coupled with the fact that ESRD patients have a MELD score of 21 with normal bilirubin and international normalized ratio (INR) [38, 39]. However, the question remains whether these patients are best served with kidney transplant alone (KTA) versus SLKT. The determination of SLKT versus KTA must be based on liver histology and signs of portal hypertension with wedge hepatic vein pressure being the gold standard [40]. In addition, long-term survival analysis showed an overall successful outcome [41, 42] with a comparable graft and patient survival rate in SLKT patients when compared with LTx or KTx alone [43]. Moreover, SLKT for polycystic disease is justified when the patient is symptomatic with dyspepsia, upper abdominal pain, and malnutrition; the liver is full of cysts; and the patient needs to have hemodialysis.

30.3 Type of Donor

The ideal cadaveric heart-beating donor for SLKT is aged < 60 years without history of kidney diseases, hypertension, and/or diabetes in stable pressure condition without or with mild dosage of vasopressor drugs. When a cadaveric donor is aged < 55 years and the body weight is more than 70 kg and the liver function tests are normal, in particular gamma-glutamyl transferases (GGT) without sign of liver steatosis at liver biopsy, part of the liver can also be suitable for SLK transplantation, splitting the liver if the donor is hemodynamically stable. More often, cadaveric heart-beating donors are extended criteria donors (ECD), and liver biopsy is mandatory to assess the liver quality especially in the case of hepatitis B virus antibody core antigen positive, moderate or severe liver steatosis, and age > 60 years; in the latter case, a kidney biopsy is also mandatory to evaluate whether the kidneys are suitable for single kidney transplant or double kidney transplant or not suitable for transplant.

30.4 Technique

30.4.1 Harvesting Procedure

The basic technique for liver procurement consists of mobilization of the liver with division of its ligaments and dissection of the bile duct, the portal vein trunk, the hepatic artery as far as the celiac triad, and the inferior vena cava above and below the liver [44]. When the heart is perfused with cardioplegic solution, the abdominal organs are washed with a hypothermic preservation solution. The liver is then removed and its vascular pedicles are definitively isolated on the bench and prepared for anastomosis. During liver removal, the dissection maneuvers must respect the anatomical structures of the liver and those of other abdominal organs, such as the kidneys. Due to the frequent hemodynamic alterations of patients with irreversible brain damage, and so as not to lose the organs if these alterations should occur during the operation, the first surgical maneuvers should aim to control the vessels which allow a rapid perfusion of the abdominal organs: the aorta and inferior mesenteric vein. Exploration of the aorta for a few centimeters immediately above the inferior mesenteric artery may reveal the presence of accessory renal polar arteries which should be left intact during the subsequent removal of the kidneys. The subhepatic inferior vena cava is then identified and divided just above the outlet of the renal veins. The kidney harvesting is performed after aorta clamping and liver removal, cutting the aorta above the iliac artery plane and opening the anterior aortic wall, dividing the renal hilum of each kidney, and separating the vena cava from the left renal vein and maintaining the right renal vein with a cava cuff to extend the length of the right renal vein, if necessary. Each ureter is preserved and harvested from the donor bladder, keeping it as long as possible with tissue to maintain vasculature and avoid ischemic problems.

30.4.2 Combined Liver and Kidney Transplantation Technique

The abdominal incision most commonly used in adult liver transplantation is the bilateral subcostal incision, extended to the left as far as the midclavicular line, to the right as far as the midaxillary line, and on the median line as far as the xiphoid cartilage (“Mercedes incision”) [45]. Hilar dissection consists of ligation of the dividing branches of the hepatic artery, followed by the common bile duct. The portal trunk is completely detached from the lymphatic tissue and is followed distally as far as the bifurcation where the vein will be ligated before the end of total hepatectomy. Mobilization of the liver continues by dividing the triangular ligaments and dividing the vena cava dorsal ligament; mobilization of the left caudate lobe from the left side of the vena cava, ligating accessory hepatic veins and mobilizing the anterior wall of the vena cava. Venous bypass [46] is routinely performed for polycystic disease: the bypass guarantees hemodynamic stability during the anhepatic stage and prevents problems connected with splanchnic and caval sequestration, in particular renal insufficiency due to venous stasis. After portal trunk clamping and

sectioning into the liver as far as possible to obtain a long stump, the vena cava is clamped with a vascular clamp above the liver, and the vena cava is divided a few centimeters inside the parenchyma; in this way first the lumen of the hepatic veins and then the caval lumen are encountered. To obtain a wide venous cuff, the outlet of the three hepatic veins is used. Caval anastomosis is performed with running suture in Prolene 4-0, according to the piggyback technique described by Tzakis et al. [47]; portal anastomosis is constructed with Prolene 6-0 running suture with growth factor described by Starzl et al. [48] followed by liver reperfusion and then arterial anastomosis with the donor common hepatic artery and recipient common hepatic artery at the level of the gastroduodenal artery outlet with Prolene 7-0 running suture. Biliary reconstruction is usually performed with an end-to-end common bile duct anastomosis over a Kehr tube with PDS 6-0 running suture. Once the laparotomy in the right upper abdomen has been closed, a Gibson incision is performed in the right or left iliac fossa to accommodate the kidney graft. After isolation of the external iliac vessels with an extraperitoneal approach, the graft renal vein is anastomosed in end-to-side fashion with the recipient external iliac vein with Prolene 6-0 running suture; the graft renal artery is anastomosed in end-to-side fashion with the recipient external iliac artery with Prolene 7-0 running suture. Ureteral anastomosis is performed with the bladder as described by the Lich-Gregoir technique with PDS 5-0 running suture with 6–12 French ureteral stent positioning.

References

1. Jain A, Reyes J, Kashyap R, et al. Long-term survival after liver transplantation in 4000 consecutive patients at a single center. Ann Surg. 2000;232(4):490–500.
2. US Multicenter FK-506 Liver Study Group. A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression in liver transplantation. N Engl J Med. 1994;331(17): 1110–5.
3. Gonwa TA, Mai ML, Melton LB, et al. End-Stage Renal Disease (ESRD) after orthotopic liver transplantation (OLTX) using calcineurin-based immunotherapy. Transplantation. 2001;72(12):1934–9.
4. Fisher NC, Nightingale PG, Gunson BK, et al. Chronic renal failure after liver transplantation: a retrospective analysis. Transplantation. 1998;66(1):59–66.
5. Klintmalm GB, Gonwa TA. Nephrotoxicity associated with cyclosporine and FK506. Liver Transpl Surg. 1995;1(5 Suppl 1):11–9.
6. Jindal RM, Popescu I. Renal dysfunction associated with liver transplantation. Postgrad Med. 1995;71:513–24.
7. Davis CL, Gonwa TA, Wilkinson AH. Identification of patients best suited for combined liver kidney transplantation: part II. Liver Transpl. 2002;8(3):193–211.
8. Chava SP, Singh B, Zaman MB, et al. Current indications for combined liver and kidney transplantation in adults. Transplant Rev (Orlando). 2009;23(2):111–9.
9. Margreiter R, Kramer R, Huber C, et al. Combined liver and kidney transplantation. Lancet. 1984;1(8385):1077–8.
10. Davis CL, Feng S, Sung R, et al. Simultaneous liver-kidney transplantation: evaluation to decision making. Am J Transplant. 2007;7:1702–9.
11. Eason JD, Gonwa TA, Davis CL, et al. Proceedings of consensus conference on simultaneous liver kidney transplantation (SLK). Am J Transplant. 2008;8:2243–51.

12. Nadim MK, Sung RS, Davis CL, et al. Simultaneous liver-kidney transplantation summit: current state and future directions. Am J Transplant. 2012;12:2901–8.
13. Brown Jr RS, Lake JR. The survival impact of liver transplantation in the MELD era, and the future for organ allocation and distribution. Am J Transplant. 2005;5:203–4.
14. Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology. 2007;45:797–805.
15. Gonwa TA, McBride MA, Anderson K, Mai ML, Wadei H, Ahsan N. Continued influence of preoperative renal function on outcome of orthotopic liver transplant (OLTX) in the US: where will MELD lead us? Am J Transplant. 2006;6:2651–9.
16. Narayanan Menon KV, Nyberg SL, Harmsen WS, et al. MELD and other factors associated with survival after liver transplantation. Am J Transplant. 2004;4:819–25.
17. Bahirwani R, Campbell MS, Siropaides T, et al. Transplantation: impact of pretransplant renal insufficiency. Liver Transpl. 2008;14:665–71.
18. Northup PG, Argo CK, Bakhru MR, Schmitt TM, Berg CL, Rosner MH. Pretransplant predictors of recovery of renal function after liver transplantation. Liver Transpl. 2010;16:440–6.
19. Cabezuelo JB, Ramirez P, Rios A, et al. Risk factors of acute renal failure after liver transplantation. Kidney Int. 2006;69:1073–80.
20. Zand MS, Orloff MS, Abt P, et al. High mortality in orthotopic liver transplant recipients who require hemodialysis. Clin Transplant. 2011;25:213–21.
21. Cassuto JR, Reese PP, Sonnad S, et al. Wait list death and survival benefit of kidney transplantation among nonrenal transplant recipients. Am J Transplant. 2010;10:2502–11.
22. Srinivas TR, Stephany BR, Budev M, et al. An emerging population: kidney transplant candidates who are placed on the waiting list after liver, heart, and lung transplantation. Clin J Am Soc Nephrol. 2010;5:1881–6.
23. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the Acute Dialysis Quality Initiative (ADQI) group. Crit Care. 2004;8:R204–12.
24. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31.
25. Jenq CC, Tsai MH, Tian YC, et al. RIFLE classification can predict short-term prognosis in critically ill cirrhotic patients. Intensive Care Med. 2007;33:1921–30.
26. Cholongitas E, Calvaruso V, Senzolo M, et al. RIFLE classification as predictive factor of mortality in patients with cirrhosis admitted to intensive care unit. J Gastroenterol Hepatol. 2009;24:1639–47.
27. du Cheyron D, Bouchet B, Parienti JJ, Ramakers M, Charbonneau P. The attributable mortality of acute renal failure in critically ill patients with liver cirrhosis. Intensive Care Med. 2005;31:1693–9.
28. O'Riordan A, Wong V, McQuillan R, McCormick PA, Hegarty JE, Watson AJ. Acute renal disease, as defined by the RIFLE criteria, post-liver transplantation. Am J Transplant. 2007;7:168–76.
29. Ferreira AC, Nolasco F, Carvalho D, et al. Impact of RIFLE classification in liver transplantation. Clin Transplant. 2010;24:394–400.
30. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39 Suppl 1:S1–266.
31. Wood RP, Ellis D, Starzel TE. The reversal of the hepatorenal syndrome in four pediatric patients following successful orthotopic liver transplantation. Ann Surg. 1987;205(4):415–9.
32. Iwatsuki S, Popovtzer MM, Goldstein G, et al. Recovery from "hepatorenal syndrome" after orthotopic liver transplantation. N Engl J Med. 1973;289(22):1155–9.
33. Koppel MH, Coburn JW, Mims MM, et al. Transplantation of cadaveric kidneys from patients with hepatorenal syndrome: evidence for the functional nature of renal failure in advanced liver disease. N Engl J Med. 1969;280(25):1367–71.

34. McGuire BM, Julian BA, Bynon S, et al. Brief communication: glomerulonephritis in patients with hepatitis C cirrhosis undergoing liver transplantation. Ann Intern Med. 2006;144(10): 735–41.
35. Morales JM, Pascual-Capdevila J, Campistol JM, et al. Membranous glomerulonephritis associated with hepatitis C virus infection in renal transplant patients. Transplantation. 1997;63(11):1634–9.
36. Cosio FG, Roche Z, Agarwal A, et al. Prevalence of hepatitis C in patients with idiopathic glomerulopathies in native and transplant kidneys. Am J Kidney Dis. 1996;28(5):752–8.
37. Kim JY, Akalin E, Dikman S, et al. The variable pathology of kidney disease after liver transplantation. Transplantation. 2010;89(2):215–21.
38. Campbell MS, Constantinescu S, Furth EE, Reddy KR, Bloom RD. Effects of hepatitis C-induced liver fibrosis on survival in kidney transplant candidates. Dig Dis Sci. 2007;52:2501–7.
39. Cooper M. Renal transplantation in ESRD with cirrhosis. Presentation at ASTS/AST/UNOS/ASN consensus conference on simultaneous liver-kidney transplantation; Sept 10–11, 2007 Chicago.
40. Ripoll C, Groszmann R, Garcia-Tsao G, Portal Hypertension Collaborative Group, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology. 2007;133:481–8.
41. Davis CL. Impact of pretransplant renal failure: when is listing for kidney-liver indicated? Liver Transpl. 2005;11(11 Suppl 2):S35.
42. Ruiz R, Kunitake H, Wilkinson AH, et al. Long-term analysis of combined liver and kidney transplantation at a single center. Arch Surg. 2006;141:735; discussion 741–2.
43. Dube GK, Cohen DJ. Simultaneous liver and kidney transplantation. Curr Opin Nephrol Hypertens. 2007;16:547.
44. Starlz TE, Hakala TR, Shaw BW, et al. A flexible procedure for multiple cadaveric organ harvesting. Surg Gynecol Obstet. 1987;165:343–8.
45. Casavilla A, Gordon RD, Starlz TE. Techniques of liver transplantation. In: Blumgart LH, editor. Surgery of the liver and biliary tract. New York: Churchill Livingstone; 1994. p. 1870–88.
46. Shaw Jr BW, Martin DJ, Marquez JM, et al. Venous bypass in clinical liver transplantation. Ann Surg. 1984;200:524–34.
47. Tzakis A, Todo S, Starzl TE. Orthotopic liver transplantation with preservation of the inferior vena cava. Ann Surg. 1989;210:649–52.
48. Starzl TE, Iwatsuki S. A growth factor in fine vascular anastomoses. Surg Gynecol Obstet. 1984;159:164–6.

Kidney-Pancreas Transplantation

31

Ugo Boggi, Piero Marchetti, and Gabriella Amorese

31.1 Introduction

Beta-cell-penic diabetic patients require insulin therapy, appropriate dietary intervention, and regular exercise in order to achieve tight metabolic control and reduce the incidence and the severity of chronic complications of diabetes [1]. Most patients do acceptably well under this therapeutic regimen, but intensive insulin treatment does not completely eliminate chronic complications and carries the significant risk of hypoglycaemia [2].

Depending on their severity, diabetic complications may be partially or totally reversed by pancreas transplantation, but their development carries negative prognostic implications. Diabetic nephropathy, in particular, decreases life expectancy [3–11]. Proteinuria alone produces a 15-fold increase in the risk of heart disease, compared with non-proteinuric diabetic patients, and a 40-fold increase, compared with the general population [4, 6]. When requiring dialysis, 75 % of insulin-dependent diabetic patients do not survive longer than 5 years [12–20].

Simultaneous pancreas-kidney (SPK) transplantation is currently considered the preferred therapeutic option in beta-cell-penic diabetic patients with end-stage renal

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failure. Some patients, however, may initially receive a renal transplant, often from a live donor, and subsequently become candidates for a pancreas after kidney transplantation.

31.2 Indications

Kidney-pancreas transplantation is indicated in diabetic patients with imminent or established end-stage renal disease [21]. The procedure renders patients free of renal failure and provides a physiological means of achieving normoglycaemia, which associates with increased life expectancy, elimination of the acute complications commonly experienced by patients with diabetes, and beneficial impact on long-term vascular complications [22, 23].

31.2.1 Diabetes and Its Burden

Diabetes is one of the most common chronic diseases in nearly all countries and continues to increase in number and significance [24, 25]. The International Diabetes Federation reports that the current prevalence of diabetes among adults aged 20–79 years in the world is of around 8 %, corresponding to more than 380 million people, increasing to 592 million people in 2035, in accordance with recent estimations [25]. The disease can be diagnosed by the use of the following criteria [24]: (a) presence of classic symptoms of hyperglycaemia or hyperglycaemic crisis and a random plasma glucose value ≥200 mg/dl (11.1 mmol/l); (b) fasting plasma glucose (FPG) value ≥126 mg/dl (7.0 mmol/l), with fasting defined as no caloric intake for at least 8 h before the test; (c) glycated haemoglobin (HbA1c) value ≥6.5 % [provided the test is performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay]; (d) 2-h plasma glucose level ≥200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. In the absence of clear symptoms of hyperglycaemia, criteria (b) to (d) should be confirmed by repeat testing. In addition, three categories of increased risk for diabetes have been identified: impaired fasting glycaemia (IFG) for FPG values of 100–125 mg/dl (5.6–6.9 mmol/l); impaired glucose tolerance (IGT), for 2-h plasma glucose on the 75-g OGTT between 140 and 199 mg/dl (7.8–11.0 mmol/l); and the situation when HbA1c value is 5.7–6.4 % [24]. For all these three conditions, risk is continuous, extending below the lower limit of the range and becoming greater at higher ends of the range [24]. On the basis of aetiology and clinical presentation, diabetes is classified into four types: type 1 (caused by autoimmune destruction of the insulin-producing beta-cells in the pancreas and representing 5–10 % of all cases), type 2 (characterized by relative insulin deficiency and insulin resistance, very often associated with obesity, and accounting for approximately 90 % of cases),

gestational diabetes (with onset or first recognition during pregnancy), and an heterogenous group identified as other specific types that includes forms due to monogenic defects leading to beta-cell failure, genetic defects in insulin action, diseases of the exocrine pancreas, endocrinopathies, drugs or chemicals, infections, uncommon forms of autoimmunity, and other genetic syndromes sometimes associated with diabetes [24].

Diabetes is associated with high morbidity and increased mortality [24, 25]. The disease enhances the risk of heart disease and stroke two- to fourfold, and 50–70 % of people with diabetes die of these events. Diabetic retinopathy is a major cause of blindness that occurs in approximately 2 % of patients after 15 years of diabetes; moreover, about 40–50 % of patients develop severe visual impairment over the years. Despite improved therapies, diabetes remains the leading cause of kidney failure, and 10–20 % of people with diabetes die of kidney failure (see also below). Diabetic neuropathy, in one or more of its several forms, affects up to 50 % of people with diabetes, and in combination with reduced blood flow, neuropathy in the feet increases up to 25-fold the chance of foot ulcers and eventual limb amputation severalfold. Finally, close to four million deaths in the 20–79 age group may be attributable to diabetes in 2010, and the proportion of deaths due to diabetes in people under 60 years of age was close to 50 % in 2013 [25].

31.2.2 The Role of Kidney-Pancreas Transplantation

It is accepted that 20–40 % of diabetic patients develop diabetic nephropathy over a period of 25 years from the diagnosis of disease, and 5–15 % progress to ESRD [24, 25]. Persistent albuminuria in the interval of 30–299 mg/24 h is considered an early stage of diabetic nephropathy in type 1 diabetes and a marker for development of nephropathy in type 2 diabetes [24]. Although evidence has been provided to show spontaneous remission of albuminuria in this category (up to 40 %) or stabilization without progressing to more elevated levels of albuminuria (≥300 mg/24 h) over 5–10 years of follow-up (30–40 %), the remaining patients will tend to move to the more significant levels of ≥300 mg/24 h and will be likely to progress to ESRD [24]. These patients will ultimately require life-sustaining, long-term renal replacement therapy, either in the form of dialysis or kidney transplantation. In the presence of type 1 diabetes, and in selected cases of type 2 diabetes, patients could benefit of a kidney-pancreas transplantation. The first kidney and pancreas transplant was performed in 1966 by William Kelly and Richard Lillehei at the University of Minnesota, USA [26]. Since then, more than 40,000 pancreas transplants have been performed worldwide [27]. Of them, >80 % have been done in patients with kidney failure who therefore have undergone a simultaneous pancreas-kidney (SPK) transplantation. In approximately 10 % of cases, a kidney transplant has been performed first, followed by a pancreas after kidney transplant (PAK) because of poor glycaemic control or progression of chronic vascular diabetic complications, including the possible development of diabetic nephropathy in the transplanted kidney. In many cases (75 % in 2012), recipients of a PAK have first undergone a living donor

kidney transplant [27]. The remaining 8–10 % of pancreas transplants (pancreas transplant alone, PTA) have been done in diabetic patients with preserved renal function, but experiencing extreme diabetes instability and/or progressive vascular diabetes complications [28, 29]. In PTA, patients may develop end-stage renal disease due to the nephrotoxic effects of immunosuppressive drugs (calcineurin inhibitor in particular), which, in turn, may lead to a subsequent kidney transplantation (around 6 % at 5 years) [29]. Renal function before PTA is a strong predictor of end-stage renal disease after PTA, with cumulative risk at 10 years increasing from 21.8 % with pre-PTA estimated glomerular filtration rate (eGFR) of ≥90 ml/min/1.73 m^2 to 52.2 % with eGFR <60 ml/min/1.73 m^2 [30]. In the SPK and PTA categories, 1- and 5-year patient survival is of around 95 % and >80 %, respectively, and the corresponding kidney graft survivals are of approximately 95 % (1 year) and 80 % (5 years) [27]. The current 1- and 5-year survival rates for the pancreatic graft are 89 and 71 % in SPK, 86 and 65 % in PAK, and 82 and 58 % in PTA, with a clear trend to further improvements [27, 28, 31–33].

31.2.3 Criteria for Kidney-Pancreas Transplantation

Since kidney-pancreas transplantation has beneficial effects on life expectancy, course of microvascular and macrovascular diabetes complications, and quality of life [27, 28, 31–33], the procedure is indicated in type 1 diabetic patients with end-stage renal disease (on dialysis or in the pre-emptive stage), in whom the risks of surgery and immunosuppression are deemed acceptable and lower than those of dialysis therapy and scarcely effective insulin therapy. Selected type 2 diabetic patients (not obese, with progressive vascular diabetic complications) can also be considered [27–29, 34]. Indications and admission criteria for kidney-pancreas transplantation in our centre, which are based on available evidence [27–29, 31–34], are as follows: end-stage renal disease (on haemodialysis or peritoneal dialysis) and type 1 diabetes [selected type 2 diabetic patients (not obese and with chronic diabetes vascular complications) may also be considered]; chronic renal failure (before dialysis – pre-emptive – with measured LOW glomerular filtration rate) and type 1 diabetes [selected type 2 diabetic patients (not obese and with chronic diabetes vascular complications) may also be considered]; severe nephrotic syndrome and type 1 diabetes [selected type 2 diabetic patients (not obese and with chronic diabetes vascular complications) may also be considered]; acceptable surgical and immunosuppressive therapy risks; appropriate psychosocial attitudes; age <60 years; the absence of additional exclusion criteria. The latter that may be permanent or temporary include HIV positivity [with the exception of admission in specific protocols [35]], neoplasms (also depending on tumour type and biology, activity, clinical and pathologic stage, duration of disease-free period), infections, severe heart diseases and/or polidistrectual atherosclerosis, severe chronic respiratory failure, liver failure, uncorrectable urinary tract abnormalities, bilateral iliac vein thrombosis, chronic coagulopathies, psychiatric diseases, mental retardation, drug addiction (including chronic ethylism), and severe obesity.

31.3 Timing

Diabetic patients do poorly under dialysis. As a consequence, the earlier the transplant, the better the result.

An analysis on 6,496 patients showed that pre-emptive SPK ($n=1,466$) was associated with an adjusted 17 % reduction (HR = 0.83; 95 % CI, 0.69–0.98; $p=0.042$) in the rate of kidney allograft failure compared to non-pre-emptive SPK. The benefit of pre-emptive SPK persisted with the composite outcome of mortality from any cause or kidney allograft loss, irrespective of the modality used to deliver chronic dialysis [36].

Becker et al. reported a registry analysis on 11,825 type I diabetic patients who underwent a first kidney transplantation alone or SPK transplantation. Most patients ($n=10,118$) had non-pre-emptive transplantation (living donor kidney = 2,438; deceased donor kidney = 3,375; deceased donor SPK = 4,305). The remaining 1,707 patients were transplanted pre-emptively (living donor kidney = 714; deceased donor kidney = 169; deceased donor SPK = 824). Pre-emptive SPK was associated with a lower risk for graft loss (adjusted risk ratio [RR] graft failure, 0.79; $p=0.01$) compared with non-pre-emptive SPK. Further, pre-emptive SPK conferred a significantly lower adjusted mortality risk [RR 0.50 ($p<0.001$)] [37].

Wiseman et al. reported an OPTN/UNOS analysis on type I diabetic recipients who received either a live donor kidney transplant ($n=1,381$) or an SPK ($n=5,441$). Overall, 2,027 patients were transplanted pre-emptively, including 1,529 SPK recipients. The remaining 4,795 patients were transplanted after initiation of chronic dialysis, including 3,912 SPK recipients (1,700 < 1 year of dialysis; 2,212 after 1–2 years of dialysis). Graft survival was improved in pre-emptive SPK (7-year unadjusted graft survival 77 %) as compared to either <1 year of dialysis SPK (70 %; $p=0.05$) or 1–2 years of dialysis SPK (73 %; $p<=0.02$). Patient survival was also improved in pre-emptive SPK (7-year unadjusted survival 89 %) as compared to either <1 year of dialysis SPK (84 %; $p=0.01$) or 1–2 years of dialysis SPK (84 %; $p<0.001$) [38].

31.4 Donor Selection

Since the results of SPK are strongly influenced by the quality of the donor, most transplant centres adopt a restrictive policy to accept pancreas grafts. However, if on one hand this policy is likely to improve the outcome of SPK in the individual patient, on the other, it widens the gap between the number of the patients on the waiting list and those who are actually transplanted. Expansion of criteria for donor acceptance should therefore be considered.

Most pancreas grafts are currently obtained from deceased, heart-beating, donors. The use of live donors has also been described [39], and donation after cardiac death is increasingly used especially in the USA [40] and in the UK [41].

The suitability of a pancreas donor is based on general criteria common to all organ procurements as well as on specific pancreas-related factors. Probably the single most relevant factor to determine pancreas suitability for transplantation is inspection by an

experienced pancreas transplant surgeon, despite being a subjective criterion that cannot be standardized. The prototype pancreas donor is a brain-dead donor, aged between 10 and 45 years, with a BMI $\leq$30 kg/m^2, who died for causes other than cerebrovascular [42, 43]. Additional factors that play a major role are duration of stay in the intensive care unit, use of high-dose vasopressors, history of cardiac arrest, and hypernatraemia. These parameters have also been used to construct risk scores for pancreas donation (i.e. the Pre-Procurement Pancreas Suitability Score [P-PASS] and the Pancreas Donor Risk Index [P-DRI]) [42, 44]. The predictive value of these scores, and hence their practical utility, remains to be determined.

Donor age is a very important variable. Very young donors are carefully considered because of the small size of the graft and the increased risk of thrombosis, because of the small size of the vessels. Most centres accept pancreas grafts from donors with a minimum weight of 30 kg. The use of donors older than 45 years, on the other hand, is known to increase the risk of technical graft failure [45].

Cause of death is another important factor. The "ideal" pancreas donor is a young trauma victim with no associated morbidity. Also young patients who died from intracranial bleeding, because of congenital cerebral aneurysm, are good pancreas donors. Death from ischemic stroke, instead, is associated with the presence of multiple comorbid factors, such as hypertension and atherosclerosis, that are known to negatively influence the result of SPK.

Hyperglycaemia, in the absence of history of diabetes, is often seen in brain-dead donors and, per se, does not contraindicate pancreas donation. Similarly, hyperamylasaemia does not necessarily correspond to pancreas damage in the absence of specific risk factors. Hyperamylasaemia is often caused by salivary gland trauma.

Vasopressors are commonly used in brain-dead donors to maintain satisfactory tissue perfusion. However, the use of powerful high-dose vasoconstrictor agents (e.g. epinephrine or norepinephrine) is considered a relative contraindication by many transplant surgeons. History of cardiac arrest, if short lived and successfully reversed, does not contraindicate pancreas donation.

Donor obesity is often considered a contraindication. In particular, grafts with fatty degeneration are considered more likely to develop posttransplant pancreatitis, thrombosis, and infection. Despite the lack of a clearly defined cutoff level, donor BMI above 30 kg/m^2 is usually considered a significant risk factor and donor BMI above 35 kg/m^2 an absolute contraindication.

Regarding organ allocation, AB0 group compatibility and negative crossmatch are usually required, while HLA matching is not critical for SPK transplants.

31.5 Surgical Techniques

31.5.1 Pancreas Procurement and Back-Table Preparation of the Graft

The University of Wisconsin solution, originally developed as a preservation solution for pancreas transplantation [46], remains the "gold standard" for preservation

of pancreas grafts. HTK [47] and Celsior [48] solutions, originally developed for cardioplegia, are also used for pancreas preservation. If cold ischaemia is maintained within 12 h, pancreas grafts are preserved equally well irrespective of the type of preservation solution.

Pancreas retrieval is usually performed in multiorgan donors. All suitable donors should be pancreas donors, irrespective of variations in hepatic vasculature. Exceptions to this rule can occur because of special needs of the liver recipient or organizational issues.

Techniques for pancreas procurement can be summarized into two main strategies: quick en bloc procurement after minimal normothermic dissection [49] and extensive warm dissection followed by individual graft retrieval [50]. The first technique is mandatory if the donor in unstable and is often preferred because of limited graft manipulation and lower risk of iatrogenic injury to both the pancreas and hepatic vasculature [49].

As previously mentioned, pancreas inspection and quality of visceral perfusion play a major role in determining pancreas suitability for transplantation. Grafts with fibrosis and/or calcification, intralobular fat, and severe oedema should be discarded.

With few exceptions, pancreas allografts are composed by the entire pancreas plus a duodenal segment. At the back table, the pancreas graft must be carefully prepared by cleaning excessive fat, preparing vascular pedicles, trimming duodenal segment, and removing the spleen.

Since the celiac trunk and the hepatic artery go with the liver, creation of a single anastomotic pedicle requires the use of a Y-bifurcated iliac graft, made of common, external, and internal donor iliac arteries. The peripheral branches of the Y-shaped graft are anastomosed end-to-end to the stumps of the superior mesenteric artery and the splenic artery. Despite the patency of one of these two large arteries that is usually sufficient to supply the entire pancreas graft and duodenal segment, variations in the origin of the dorsal pancreatic artery and intraparenchymal vasculature can produce segmental graft infarction after occlusion of one large arterial pedicle. To verify the presence of valid collateral circulation, a small amount of preservation solution can be injected in one of the two arteries. Brisk backflow from the other arterial pedicle, as well as outflow from the portal vein, indicates satisfactory collateral circulation. The absence of arterial backflow requires revascularization of the gastroduodenal artery [51].

The duodenal segment is trimmed at the appropriate length and closed by a stapler. Closures are reinforced and inverted. We prefer to place a Foley catheter in the duodenal segment to provide temporary drainage of pancreatic juice after reperfusion in order to avoid duodenal overdistension [49].

31.5.2 Graft Implantation

Most of the surgical challenges associated with pancreas transplantation revolve around the high risk of vascular thrombosis and the difficult management of exocrine secretions. Despite improved results, no surgical technique, and even no single

surgical step, has achieved universal acceptance [52]. The incision is usually a midline laparotomy, but the two grafts can also be transplanted through two separate iliac, hockey stick, incisions. The graft can be placed "head up" or "head down", in the pelvis, right flank region, or over the mesenteric root. Venous effluent can be achieved either in the portal or systemic circulation.

Typically, the pancreas is transplanted on the right side, because of the more convenient venous anatomy, and the kidney on the left iliac fossa. Ipsilateral SPK transplantation can also be accomplished, to spare one iliac axis or because of specific recipient needs. Exocrine secretions can be drained in the bladder or in the gut. Enteric drainage occurs in the small bowel either directly or through a Roux-en-Y loop. Newer techniques include direct anastomosis with recipient duodenum [53] or stomach [54]. Alleged advantages of these methods include direct access to donor duodenum for endoscopic biopsy, but concerns remain on safety, especially when recipient duodenum is involved, if allograft pancreatectomy becomes necessary.

Recently, we have described the technique for laparoscopic robot-assisted, pancreas transplantation including SPK transplantation [55, 56]. The advantages of a minimally invasive approach would seem obvious in the fragile diabetic recipient, but safety and efficacy of this newer technique need to be further assessed.

Kidney transplantation employs standard techniques, but if performed through a transperitoneal approach, the graft should be fixed in order to avoid twisting around the renal pedicle [57].

Cold ischaemia time exceeding 20 h has long been recognized a negative prognostic factor for the occurrence of surgical complications after pancreas transplantation. A growing burden of evidence shows that cold ischaemia time should actually be reduced to 12 h or less, especially when using less than ideal donors [43].

31.6 Postoperative Management and Outcome

31.6.1 Immunosuppression

Despite recent improvements, the results of pancreas transplantation continue to be challenged by high rejection rates [58]. Because of this concern, the use of T-cell depleting antibody induction is often employed.

Maintenance immunosuppression regimens are based on steroids, tacrolimus, and mycophenolate in more than 80 % of cases [59, 60]. The switching to cyclosporine and/or mammalian target of rapamycin is considered to reverse the side effects related to the standard regimen or under individual circumstances [61, 62].

31.6.2 Postoperative Care

After the transplant, recipients are monitored in the postanaesthesia care unit or intensive care unit. Ventilatory and haemodynamic assessment is paramount during recovery. A complete blood count, complete chemistry, coagulation profiles, chest

radiograph, and EKG are routinely obtained. Vital signs, oxygen saturation, and urine output are checked frequently. The first 24–48 h posttransplant is of overwhelming importance.

During this early period most of the efforts are focused to avoid vascular thrombosis. Although there is no agreed protocol for anticoagulant prophylaxis, most centres use early heparin infusion followed by oral antiplatelet agents. Antimicrobial, antifungal, and antiviral prophylaxis are also used routinely.

31.6.3 Major Posttransplant Complications

The propensity of the pancreas to vascular thrombosis, the need to manage exocrine secretions, and the high burden of medical comorbidities associated with diabetes and uraemia have all compounded the historical high rate of early complications after pancreas transplantation. Despite not all these complications are caused by a surgical error or misadventure, they are usually referred to as "surgical complications" because they often require surgical reintervention. Incidence has declined over time, but approximately 20 % of recipients still require at least one relaparotomy after pancreas transplantation [63]. Surgical complications remain the leading cause of early graft loss [64], now occurring in less than 5 % of pancreas transplants [63]. Graft survival, but not patient survival, is reduced by surgical complications [63].

The risk of major, potentially life-threatening, complications persists long term in fewer than 3 % of recipients in the form of pseudoaneurysm or arterioenteric fistula [65]. Chronic rejection may trigger these catastrophes [66, 67].

31.6.4 Follow-Up

Follow-up is key to the success of all solid organ transplants and in particular to SPK which couples the challenges of all other transplants (i.e. therapeutic noncompliance, infections, rejection, etc.) to the specific challenges posed by transplanting diabetic patients (i.e. presence of established secondary complications, risk of autoimmune reactivation, etc.). In a modern transplant centre, follow-up after SPK should be multidisciplinary.

In the early posttransplant period, follow-up focuses on prevention of vascular thrombosis, prevention and treatment of infections, achievement and maintenance of therapeutic drug levels, and monitoring for rejection. The lack of reliable markers for pancreas rejection remains a major issue. When pancreatic rejection is suspected, despite seemingly good renal function, pancreas biopsy is the only tool to achieve a reliable diagnosis.

In the long-term period, besides all needs associated with the follow-up of kidney transplant recipients, SPK recipients should be followed up regarding the evolution of secondary complications of diabetes. Death with functioning grafts remains a major issue in the long-term period. SPK recipients should therefore be strongly

encouraged to adopt a healthy lifestyle, in order to reduce their inherent high cardiovascular risk profile.

Recent evidence suggests also the need, besides standard immunologic follow-up, to closely monitor SPK with regard to de novo donor-specific anti-HLA antibodies [68].

Recurrence of autoimmunity is a further possibility that should be born in mind in this recipient population, as it could occur much more frequently than previously believed [31].

31.6.5 Outcome

Patient and graft survival rate for primary SPK transplant constantly improved over the last several years and now exceed 95 and 85 %, respectively [69]. The half-life of pancreas grafts now averages 16.7 years, achieving the longest duration found among extrarenal grafts [70] and nearly matching that of renal grafts from deceased donors [71].

Infection is the leading cause of death in the early posttransplant period, while cardiovascular events become prevalent long term. Other relevant causes of death are haemorrhage and malignancy [69].

Graft loss has a strong impact on the relative risk (RR) of recipient death. When the renal graft fails, the RR of recipient death increases almost 11-fold. When the pancreas fails, the RR of recipient death increases almost threefold. The RR of recipient death is also increased by patient age (≥45 years) and the need for pre-transplant dialysis or previous kidney transplant [69].

Vascular complications, intra-abdominal infections, and graft pancreatitis can cause pancreas loss, but the leading cause of pancreas failure remains rejection [72, 73]. Autoimmunity can also induce graft loss [74–77].

The diagnosis of pancreatic rejection can be proven only by core biopsy. A rise in serum creatinine can herald pancreatic rejection (the so-called sentinel kidney), but isolated pancreatic rejection has also been described [78]. An increase in serum amylase and lipase can be a further sign of pancreatic rejection, but it is not specific. Hyperglycaemia reflects islet destruction or severe isleitis and, as such, is a very late marker of rejection.

Antibody-mediated rejection (AMR) can also occur [79]. Pancreatic AMR is a combination of serological and immunohistological findings consisting of DSA detection, morphological evidence of microvascular injury, and C4d staining in interacinar capillaries.

Recurrence of autoimmune disease can also occur despite immunosuppression [75, 80]. A possible interplay between AMR and autoimmune recurrence has also been described [80, 81]. Recurrence of autoimmunity occurs with isolated hyperglycaemia, without functional impairment of renal allograft or elevation of pancreatic enzymes. In these patients, islet cell autoantibodies against GAD, IA-2, and ZnT8 antigens have persisted, have increased, or have reappeared after pancreas transplantation [74, 75, 77]. These antibodies are accompanied by circulating

autoreactive CD4 or CD8 T cells. Biopsy shows insulitis and beta-cell loss without the features typically associated with allograft rejection. The rise of autoantibodies precedes hyperglycaemia by several years. Treatment options are nonspecific and include more sophisticated immunosuppressive therapies to target T cells, B cells, and autoantibodies. Plasmapheresis may also be used [74, 75].

31.6.6 Infections and Malignancies

Despite improved results, malignancies and bacterial, viral, and fungal infections remain a significant cause of mortality and morbidity [82].

The occurrence of viral infections may be facilitated to the fact that most diabetic patients have an impaired immune system and may not produce antibodies against cytomegalovirus and Epstein-Barr virus [83].

Posttransplant proliferative disorder (PTLD) is the most common malignancy after SPK, but the incidence of other cancers is also increased being three- to fourfold higher compared with matched and healthy population [84]. The cumulative incidence of PTLD from SRTR/Annual Data Report at 4 years is 0.9 % after SPK [58].

Polyomavirus (BK) can induce a severe nephropathy (BKVN) and is an important cause of renal graft loss following SPK. Routine screening for BK viraemia and an early treatment in case of positivity may protect from BKVN development. Recent data have shown that CNI and mycophenolate reduction and introduction of leflunomide may be important to block BK reactivation [85].

References

1. Diabetes Complications and Control Trial Research Group. The effect of intensive insulin treatment of diabetes on the development and progression of long-term complications of insulin dependent diabetes mellitus. N Engl J Med. 1993;329:977–86.
2. Kendall DM, Bergenstal RM. Limitations of nontransplant treatment options for Type 1 diabetes mellitus. In: Gruessner RWG, Sutherland DER, editors. Transplantation of the pancreas. New York: Springer; 2004. p. 29–38.
3. Allen KV, Walker JD. Microalbuminuria and mortality in long duration type 1 diabetes. Diabetes Care. 2003;26:2389–91.
4. Borch-Johnsen K, Kreiner S. Proteinuria: value as predictor of cardiovascular mortality in insulin dependent diabetes mellitus. Br Med J (Clin Res Ed). 1987;294:1651–4.
5. Warram JH, Laffel LMB, Ganda OP, Christlieb AR. Coronary artery disease is the major determinant of excess mortality in patients with insulin-dependent diabetes mellitus and persistent proteinuria. J Am Soc Nephrol. 1992;3:S104–10.
6. Borch-Johnsen K, Andersen PK, Deckert T. The effect of proteinuria on relative mortality in type I (insulin-dependent) diabetes. Diabetologia. 1985;28:590–6.
7. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999;341:1725–30.
8. Kroslewski AS, Kosinski EJ, Warram JH, Leland OS, Busick EJ, Asmal AC, et al. Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. Am J Cardiol. 1987;59:750–5.

9. Weinrauch LA, D'Elia JA, Healy RW, Gleason RE, Takacs FJ, Libertino JA, et al. Asymptomatic coronary artery disease: angiographically in diabetic patients before renal transplantation: relation of findings to postoperative survival. Ann Intern Med. 1978;88:346–8.
10. Braun WE, Phillips DF, Vidt DG, et al. Coronary artery disease in 100 diabetics with end-stage renal failure. Transplant Proc. 1984;16:603–7.
11. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, et al. Diabetes and cardiovascular disease: a statement of healthcare professionals from the American Heart Association. Circulation. 1999;100:1134–46.
12. Gruessner RW, Sutherland DE, Gruessner AC. Mortality assessment for pancreas transplants. Am J Transplant. 2004;4:2018–26.
13. Venstrom JM, McBride MA, Rother KI, Hirshberg B, Orchard TJ, Harlan DM. Survival after pancreas transplantation in patients with diabetes and preserved kidney function. JAMA. 2003;290:2817–23.
14. Tydén G, Tollemar J, Bolinder J. Combined pancreas and kidney transplantation improves survival in patients with end-stage diabetic nephropathy. Clin Transplant. 2000;14:505–8.
15. Becker BN, Brazy PC, Becker YT, Odorico JS, Pintar TJ, Collins BH, et al. Simultaneous pancreas-kidney transplantation reduces excess mortality in type I diabetic patients with end-stage renal disease. Kidney Int. 2000;57:2129–35.
16. Smets YF, Westendorp RG, van der Pjil JW, de Charro FT, Ringers J, de Fijter JW, et al. Effect of simultaneous pancreas- kidney transplantation on mortality of patients with type I diabetes mellitus and end-stage renal failure. Lancet. 1999;353:1915–9.
17. Ojo AO, Meier-Kriesche HU, Hanson JA, Leichtman A, Magee JC, Cibrik D, et al. The impact of simultaneous pancreas-kidney transplantation on long-term patient survival. Transplantation. 2001;71:82–90.
18. Navarro X, Kennedy WR, Aeppli D, Sutherland DE. Neuropathy and mortality in diabetes: influence of pancreas transplantation. Muscle Nerve. 1996;19:1009–16.
19. Shapiro R, Corry RJ, Thai N. Outcomes after pancreatic transplantation. In: Corry RJ, Shapiro R, editors. Pancreatic transplantation. New York: Informa Healthcare; 2007. p. 1–10.
20. Reddy KS, Stablein D, Taranto S, Stratta RJ, Johnston TD, Waid TH, et al. Long-term survival following simultaneous kidney pancreas transplantation versus kidney transplantation alone in patients with type 1 diabetes mellitus and renal failure. Am J Kidney Dis. 2003;41:464–70.
21. Robertson RP, Davis C, Larsen J, Stratta R, Sutherland DE, American Diabetes Association. Pancreas and islet transplantation in type 1 diabetes. Diabetes Care. 2006;29(4):935.
22. Kaufman DB, Sutherland DE. Simultaneous pancreas-kidney transplants are appropriate in insulin-treated candidates with uremia regardless of diabetes type. Clin J Am Soc Nephrol. 2011;6(5):957–9.
23. Boggi U, Rosati CM, Marchetti P. Follow-up of secondary diabetic complications after pancreas transplantation. Curr Opin Organ Transplant. 2013;18(1):102–10.
24. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37 Suppl 1:S81–90.
25. www.idf.org
26. Kelly WD, Lillehei RC, Merkel FK, Idezuki Y, Goetz FC. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. Surgery. 1967;61(6):827–37.
27. Gruessner RW, Gruessner AC. The current state of pancreas transplantation. Nat Rev Endocrinol. 2013;9(9):555–62.
28. Boggi U, Vistoli F, Amorese G, Giannarelli R, Coppelli A, Mariotti R, Rondinini L, Barsotti M, Signori S, De Lio N, Occhipinti M, Mangione E, Cantarovich D, Del Prato S, Mosca F, Marchetti P. Long-term (5 years) efficacy and safety of pancreas transplantation alone in type 1 diabetic patients. Transplantation. 2012;93(8):842–6.
29. Gruessner RW, Gruessner AC. Pancreas transplant alone: a procedure coming of age. Diabetes Care. 2013;36(8):2440–7.
30. Kim SJ, Smail N, Paraskevas S, Schiff J, Cantarovich M. Kidney function before pancreas transplant alone predicts subsequent risk of end-stage renal disease. Transplantation. 2014;97(6):675–80.

31. Boggi U, Vistoli F, Egidi FM, Marchetti P, De Lio N, Perrone V, Caniglia F, Signori S, Barsotti M, Bernini M, Occhipinti M, Focosi D, Amorese G. Transplantation of the pancreas. Curr Diab Rep. 2012;12(5):568–79.
32. White SA, Shaw JA, Sutherland DE. Pancreas transplantation. Lancet. 2009;373(9677): 1808–17.
33. Larsen JL. Pancreas transplantation: indications and consequences. Endocr Rev. 2004;25(6):919–46.
34. Orlando G, Stratta RJ, Light J. Pancreas transplantation for type 2 diabetes mellitus. Curr Opin Organ Transplant. 2011;16(1):110–5.
35. Grossi PA, Righi E, Gasperina DD, Donati D, Tozzi M, Mangini M, Astuti N, Cuffari S, Castelli P, Carcano G, Dionigi G, Boggi U, Costa AN, Dionigi R. Report of four simultaneous pancreas-kidney transplants in HIV-positive recipients with favorable outcomes. Am J Transplant. 2012;12(4):1039–45.
36. Israni AK, Feldman HI, Propert KJ, Leonard M, Mange KC. Impact of simultaneous kidney-pancreas transplant and timing of transplant on kidney allograft survival. Am J Transplant. 2005;5:374–82.
37. Becker BN, Rush SH, Dykstra DM, Becker YT, Port FK. Preemptive transplantation for patients with diabetes-related kidney disease. Arch Intern Med. 2006;166:44–8.
38. Wiseman AC, Huang E, Kamgar M, Bunnapradist S. The impact of pre-transplant dialysis on simultaneous pancreas-kidney versus living donor kidney transplant outcomes. Nephrol Dial Transplant. 2013;28:1047–58.
39. Boggi U, Amorese G, Marchetti P, Mosca F. Segmental live donor pancreas transplantation: review and critique of rationale, outcomes, and current recommendations. Clin Transplant. 2011;25:4–12.
40. Siskind E, Akerman M, Maloney C, Huntoon K, Alex A, Siskind T, Bhaskeran M, Ali N, Basu A, Molmenti E, Ortiz J. Pancreas transplantation from donors after cardiac death: an update of the UNOS database. Pancreas. 2014;43:544–7.
41. Johnson RJ, Bradbury LL, Martin K, Neuberger J, UK Transplant Registry. Organ donation and transplantation in the UK-the last decade: a report from the UK national transplant registry. Transplantation. 2014;97 Suppl 1:S1–27.
42. Finger EB, Radosevich DM, Dunn TB, Chinnakotla S, Sutherland DE, Matas AJ, Pruett TL, Kandaswamy R. A composite risk model for predicting technical failure in pancreas transplantation. Am J Transplant. 2013;13:1840–9.
43. Maglione M, Ploeg RJ, Friend PJ. Donor risk factors, retrieval technique, preservation and ischemia/reperfusion injury in pancreas transplantation. Curr Opin Organ Transplant. 2013;18:83–8.
44. Vinkers MT, Rahmel AO, Slot MC, Smits JM, Schareck WD. How to recognize a suitable pancreas donor: a Eurotransplant study of preprocurement factors. Transplant Proc. 2008;40:1275–8.
45. Gruessner AC, Barrou B, Jones J, Dunn DL, Moudry-Munns K, Najarian JS, Sutherland DE, Gruessner RW. Donor impact on outcome of bladder-drained pancreas transplants. Transplant Proc. 1993;25:3114–5.
46. Wahlberg JA, Love R, Landegaard L, Southard JH, Belzer FO. 72-hour preservation of the canine pancreas. Transplantation. 1987;43:5–8.
47. Fridell JA, Mangus RS, Powelson JA. Histidine-tryptophan-ketoglutarate for pancreas allograft preservation: the Indiana University experience. Am J Transplant. 2010;10:1284–9.
48. Boggi U, Vistoli F, Del Chiaro M, Signori S, Croce C, Pietrabissa A, Berchiolli R, Marchetti P, Del Prato S, Mosca F. Pancreas preservation with University of Wisconsin and Celsior solutions: a single-center, prospective, randomized pilot study. Transplantation. 2004;77: 1186–90.
49. Boggi U, Vistoli F, Del Chiaro M, Signori S, Pietrabissa A, Costa A, Bartolo TV, Catalano G, Marchetti P, Del Prato S, Rizzo G, Jovine E, Pinna AD, Filipponi F, Mosca F. A simplified technique for the en bloc procurement of abdominal organs that is suitable for pancreas and small-bowel transplantation. Surgery. 2004;135:629–41.

50. Wunderlich H, Brockmann JG, Voigt R, Rauchfuss F, Pascher A, Brose S, Binner C, Bittner H, Klar E, Commission of Organ Donation and Removal German Transplantation Society. DTG procurement guidelines in heart beating donors. Transpl Int. 2011;24:733–57.
51. Boggi U, Amorese G, Marchetti P. Surgical techniques of pancreas transplantation. In: Hakim NS, Stratta RJ, Gray D, Friend P, Colman A, editors. Pancreas, islet, and stem cell transplantation for diabetes. 2nd ed. Oxford: Oxford University Press; 2010. p. 111–35.
52. Demartines N, Schiesser M, Clavien PA. An evidence-based analysis of simultaneous pancreas-kidney and pancreas transplantation alone. Am J Transplant. 2005;5:2688–97.
53. De Roover A, Coimbra C, Detry O, Van Kemseke C, Squifflet JP, Honore P, Meurisse M. Pancreas graft drainage in recipient duodenum: preliminary experience. Transplantation. 2007;84:795–7.
54. Shokouh-Amiri H, Zakhary JM, Zibari GB. A novel technique of portal-endocrine and gastric-exocrine drainage in pancreatic transplantation. J Am Coll Surg. 2011;212:730–8.
55. Boggi U, Signori S, Vistoli F, D'Imporzano S, Amorese G, Consani G, et al. Laparoscopic robot-assisted pancreas transplantation: first world experience. Transplantation. 2012;93:201–6.
56. Boggi U, Signori S, Vistoli F, Amorese G, Consani G, De Lio N, et al. Current perspectives on laparoscopic robot-assisted pancreas and pancreas-kidney transplantation. Rev Diabet Stud. 2011;8:28–34.
57. West MS, Stevens RB, Metrakos P, Foshager MC, Jessurun J, Sutherland DE, Gruessner RW. Renal pedicle torsion after simultaneous kidney-pancreas transplantation. J Am Coll Surg. 1998;187:80–7.
58. OPTN/SRTR annual data report 2010/Pancreas. p. 34–52.
59. Heilman RL, Mazur MJ, Reddy KS. Immunosuppression in simultaneous pancreas-kidney transplantation: progress to date. Drugs. 2010;70:793–804.
60. Singh RP, Stratta RJ. Advances in immunosuppression for pancreas transplantation. Curr Opin Organ Transplant. 2008;13:79–84.
61. Matias P, Araujo MR, Romao JE, Abensur H, Noronha IL. Conversion to sirolimus in kidney-pancreas and pancreas transplantation. Transplant Proc. 2008;40:3601–5.
62. Egidi MF, Cowan PA, Naseer A, Gaber AO. Conversion to sirolimus in solid organ transplantation: a single-center experience. Transplant Proc. 2003;35:S131–7.
63. Banga N, Hadjianastassiou VG, Mamode N, Calder F, Olsburgh J, Drage M, et al. Outcome of surgical complications following simultaneous pancreas–kidney transplantation. Nephrol Dial Transplant. 2012;27:1658–63.
64. Fernandez-Cruz L, Ricart MJ, Astudillo E, Sabater L, Fondevila C, Prados M. Enteric drainage as primary procedure and after cystoenteric conversion in whole pancreaticoduodenal transplantation. Transplant Proc. 1997;29:643–4.
65. Fridell JA, Johnson MS, Goggins WC, Beduschi T, Mujtaba MA, Goble ML, et al. Vascular catastrophes following pancreas transplantation: an evolution in strategy at a single center. Clin Transplant. 2012;26:164–72.
66. Higgins PD, Umar RK, Parker RJ, DiMagno MJ. Massive lower gastrointestinal bleeding after rejection of pancreatic transplants. Nat Clin Pract Gastroenterol Hepatol. 2005;2:240–4.
67. Lopez NM, Jeon H, Ranjan D, Johnston TD. Atypical etiology of massive gastrointestinal bleeding: arterio-enteric fistula following enteric drained pancreas transplant. Am Surg. 2004;70:529–32.
68. Mittal S, Page SL, Friend PJ, Sharples EJ, Fuggle SV. De novo donor-specific HLA antibodies: biomarkers of pancreas transplant failure. Am J Transplant. 2014;14:1664–71.
69. Gruessner AC, Sutherland DER. In: Hakim NS, Stratta RJ, Gray D, Friend P, Colman A, editors. Pancreas-transplant outcomes for United States (US) cases as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR). New York: Oxford University Press; 2010. p. 299–315.
70. Lodhi SA, Lamb KE, Meier-Kriesche HU. Solid organ allograft survival improvement in the United States: the long-term does not mirror the dramatic short-term success. Am J Transplant. 2011;11:1226–35.

71. Seron D, Moreso F, Arias M, Campistol JM, Curto J, Hernandez D, et al. Estimation of renal allograft half-life: fact or fiction? Nephrol Dial Transplant. 2011;26:3013–8.
72. Oberholzer J, Tzvetanov G, Benedetti E. Surgical complication of pancreas transplantation. In: Hakim NS, Stratta RJ, Gray D, Friend P, Colman A, editors. Pancreas, islet, and stem cell transplantation for diabetes. New York: Oxford University Press; 2010. p. 179–89.
73. Troxell ML, Koslin DB, Norman D, Rayill S, Mittalhenkle A. Pancreas allograft rejection: analysis of concurrent renal allograft biopsies and posttherapy follow-up biopsies. Transplantation. 2010;90:75–84.
74. Burke 3rd GW, Vendrame F, Pileggi A, Ciancio G, Reijonen H, Pugliese A. Recurrence of autoimmunity following pancreas transplantation. Curr Diabetes Rep. 2011;11:413–9.
75. Vendrame F, Pileggi A, Laughlin E, Allende G, Martin-Pagola A, Molano RD, et al. Recurrence of type 1 diabetes after simultaneous pancreas-kidney transplantation, despite immunosuppression, is associated with autoantibodies and pathogenic autoreactive CD4 T-cells. Diabetes. 2010;59:947–57.
76. Braghi S, Bonifacio E, Secchi A, Di Carlo V, Pozza G, Bosi E. Modulation of humoral islet autoimmunity by pancreas allotransplantation influences allograft outcome in patients with type 1 diabetes. Diabetes. 2000;49:218–24.
77. Occhipinti M, Lampasona V, Vistoli F, Bazzigaluppi E, Scavini M, Boggi U, et al. Zinc transporter 8 autoantibodies increase the predictive value of islet autoantibodies for function loss of technically successful solitary pancreas transplant. Transplantation. 2011;92:674–7.
78. Shapiro R, Jordan ML, Scantlebury VP, Vivas CA, Jain A, McCauley J, et al. Renal allograft rejection with normal renal function in simultaneous kidney/pancreas recipients: does dissynchronous rejection really exist? Transplantation. 2000;69:440–1.
79. Drachemberg CB, Torrealba JR, Nankivell BJ, Rangel EB, Bajema IM, Kim DU, et al. Guidelines for the diagnosis of antibody- mediated rejection in pancreas allografts-updated banff grading schema. Am J Transplant. 2011;11:1792–802.
80. Pugliese A, Reijonen HK, Nepom J, Burke 3rd GW. Recurrence of autoimmunity in pancreas transplant patients: research update. Diabetes Manag (Lond). 2011;1:229–38.
81. Porcheray F, DeVito J, Yeap BY, Xue L, Dargon I, Paine R, et al. Chronic humoral rejection of human kidney allografts associated with broad autoantibody response. Transplantation. 2010;89:1239–46.
82. Rostambeigi N, Kudva YC, John S, Mailankody S, Pedersen RA, Dean PG, et al. Epidemiology of infections requiring hospitalization during long-term follow-up of pancreas transplantation. Transplantation. 2010;89:1126–33.
83. Parsaik AK, Bhalla T, Dong M, Rostambeigi N, Dierkhising RA, Dean P, et al. Epidemiology of cytomegalovirus infection after pancreas transplantation. Transplantation. 2011;92:1044–50.
84. Girman P, Lipar K, Kocik M, Kriz J, Marada T, Saudek F. Neoplasm incidence in simultaneous pancreas and kidney transplantation: a single-center analysis. Transplant Proc. 2011;43:3288–91.
85. Mujtaba M, Fridell J, Sharfuddin A, Kandula P, Yaqub MS, Phillips CL, et al. BK virus nephropathy in simultaneous pancreas kidney transplant: a potentially preventable cause of kidney allograft loss. Clin Transplant. 2012;12:87–93.