Organ Transplantation

TEDOR

Transeuropean Educational initiative in Organ Donation and Transplantation

THE PROJECT

The TEODOR project was a 36-month initiative funded by the European Commission's Erasmus+ program. It was led by the Pauls Stradiņš Clinical University Hospital and Latvijas Universitate, in collaboration with prestigious institutions such as the Universitat de Barcelona and DTI Foundation from Spain, the National Transplant Office of the Ministry of Health from Lithuania, Fakultní nemocnice Královské Vinohrady from the Czech Republic, and Karolinska University Hospital from Sweden. The main goal of the TEODOR project was to create a new training program on organ donation and transplantation. This program was specifically designed for doctors and healthcare personnel in Latvia, the Czech Republic, and Lithuania.

This ebook contains information prepared for the TEODOR training program, with a dedicated focus on organ transplantation. The content within covers a wide array of relevant topics, intended to equip healthcare professionals with essential knowledge and expertise in this critical area. By disseminating this information, the ebook aims to improve organ transplantation practices and ultimately enhance patient care and outcomes across the participating countries.

TEODOR
Transeuropean Educational initiative in Organ Donation and Transplantation

DTI
DONATION & TRANSPLANTATION INSTITUTE

Co-funded by the Erasmus+ Programme of the European Union

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INTRODUCTION

Our human body, "the host," suffers millions of attacks from exogenous (outside the body) and endogenous (inside the body) factors that can cause harm to our daily functioning.

We possess a unique system, the immune system, which protects us on different levels and in different ways. It consists of highly mobile complex cell systems, proteins and amino acids that recognize, prepare and eliminate the foreign factors.

This immune system provides 3 different ways of protection:

- Surveillance: recognition of foreign antigens sitting on cell or micro-organism membranes.
- Defence: non-specific and specific mechanisms that destroy and remember foreign intruders.
- Homeostasis: the possibility and capacity of maintaining a balance between protection and destruction within the system.

1. ALLOGENEIC RECOGNITION

Why is there an immunologic response to organ transplantation from individuals of the same species?

In the human body, some proteins are polymorphic.

Polymorphic means that there are some proteins with small differences in the amino acid sequence between individuals, although they correctly perform the same role in each individual.

The polymorphic proteins of another individual are recognized as foreign by the immune system, and trigger a response aimed at elimination of the grafted organ with polymorphic differences (alloresponse).

There are several polymorphic proteins in the human body, but HLA proteins are particularly important in allogeneic response for three reasons (Table 1).

Table 1. HLA proteins

HLA proteins...	Consequences
are expressed on the cell membrane	In living cells, membrane HLA is available for circulating antibodies and T cell receptor binding
are extremely polymorphic	There are hundreds of alleles. The possibility of the donor and recipient sharing alleles is highly infrequent, except for siblings (25% in each pregnancy)
Their function is to interact with T cell receptors	T cell receptors are able to distinguish small changes in donor HLA amino acid sequences

The high degree of polymorphism, the expression in membrane and the physiological function of HLA molecules determine that grafted organs are recognized as foreign by the recipient's immune system. This recognition triggers an immunological rejection response that includes antibody (alloantibody) formation and the expansion of cytotoxic T lymphocytes (CTL).

Are HLA proteins the only molecules involved in organ rejection?

ABO blood groups are also polymorphic, and differences between individuals are due to different carbohydrates in cell membranes. Due to natural anti-ABO antibodies, only organs with ABO compatibility between donor and recipient are usually transplanted. In some receptors with low levels of natural anti-ABO antibodies their removal is possible, and kidneys can be transplanted with an acceptable survival rate. The RhD blood group does not constitute a difficulty in solid organ transplantation since these molecules are expressed only in erythrocytes, not in endothelial or parenchymal cells.

Classes of HLA molecules

There are two classes of HLA molecules with different distribution and function (Table 2).

Table 2. Two classes of HLA molecules with different distribution and function

Class	HLA-Class I	HLA-Class II
Expression	All cells (except red cells)	Macrophages, dendritic cells, Langerhans, Kupffer, some endothelia, B lymphocytes
Chains	Alpha; highly polymorphic + Beta 2 microglobulin invariant	Beta: highly polymorphic + Alpha: with few polymorphisms
Locus	HLA-A, HLA-B, HLA-C	HLA-DRB1+DRBA, HLA-DRB3/4/5+DRBA, HLA-DQA1+HLA-DQB1, HLA-DPA1+HLA-DPB1
Presents	Intracellular antigens (e.g., virus)	Exogenous foreign antigens (e.g., bacteria)
Induce in Tx Recipient	Cytotoxic response (CTL) and antibodies	Activation of helper T lymphocytes and antibodies
Tx Recipient	Cytotoxic response (CTL) and antibodies	Activation of helper T lymphocytes and antibodies

Physiologically, HLA molecules are the "tray" into which the antigen presenting cells (APC) introduce foreign antigens to T lymphocytes, which is also the way that virus-infected cells present viral peptides to cytotoxic T cells (CTL). This function determines the peculiar response that HLA triggers in the recipient of an allogeneic organ and explains why some memory cells that remember previous viral infection (recipient HLA + viral peptide) can react with donor HLA molecules.

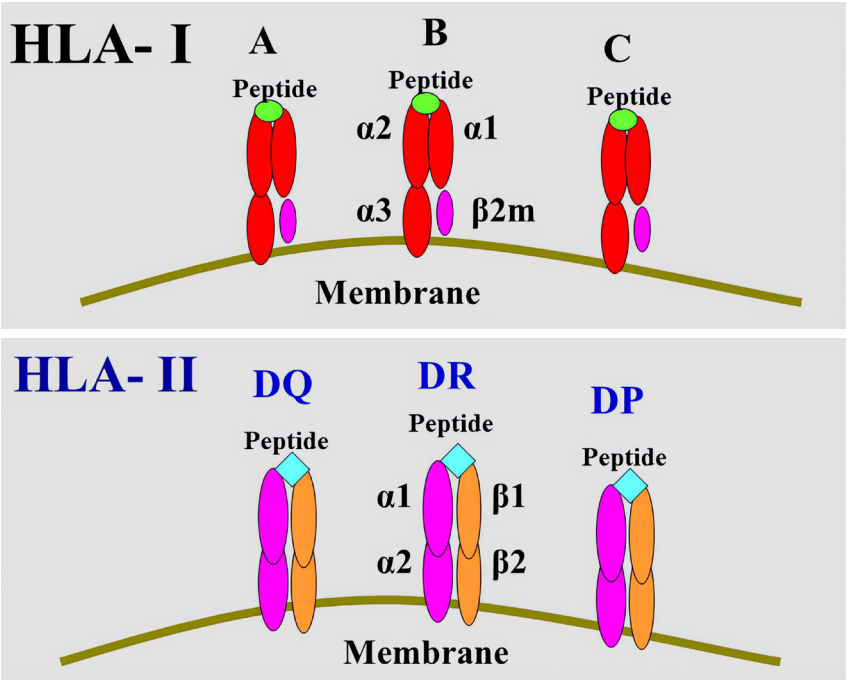

Figure 1. HLA I & HLA II.

Inheritance of HLA molecules

The short arm of each chromosome 6 bears one allele corresponding to different possible genes for a particular locus. All the genes in one chromosome inherited in block from a progenitor are known as a "haplotype". Siblings can inherit the same haplotypes from their father and mother, and therefore be HLA identical. Identical HLA in a random population is highly infrequent.

Each individual expresses two alleles encoding a protein for each locus. These alleles are identified by the letter that identifies the locus, followed by several groups of digits separated by a colon ":" (e.g., A*23:01:01).

An example typing would be:

Haplotype from mother: A*01:01, C*06:02, B*08:01, DRB1*03:01, DQB1*02:01

Haplotype from father: A*02:01, C*07:01, B*50:01, DRB1*07:01. DQB1*03:03

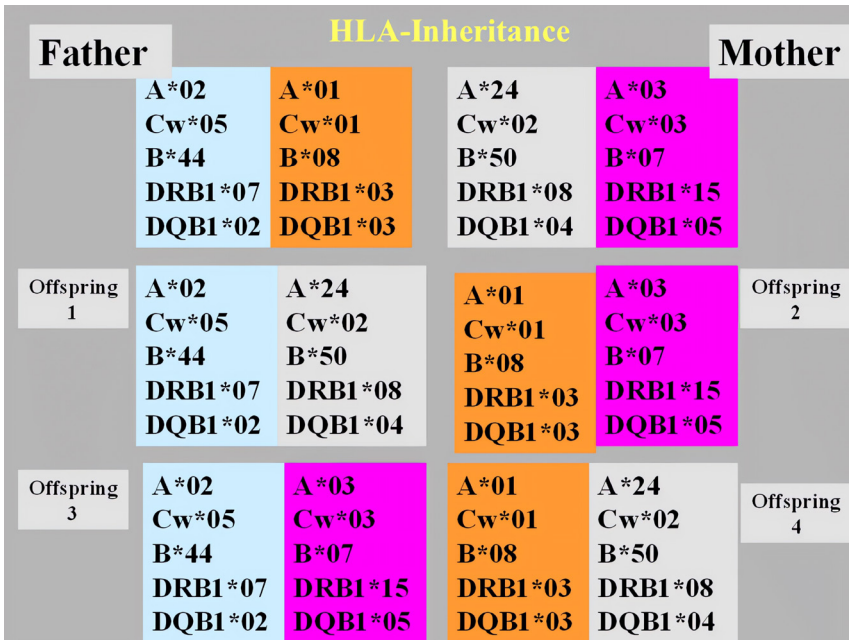

Figure 2. HLA-Inheritance.

How is an HLA allele named?

As the number of alleles is extremely high, similar alleles are grouped for practical reasons:

Groups are defined only by the first field. (e.g., A*23 identifies: A*23:01:01 and A*23:01:02 and A*23:01:03 and A*23:01:04, etc.) and are designed as "low resolution typing", of which an example would be, A*01, A*02; B*08, B*50; C*06, C*07; DRB1*03, DRB1*07; DQB1*02; DQB1*03.

When more than one field (group of digits) is used for typing, it is called "high resolution typing". Each group is separated by a colon ":" (e.g., A*11:03; B*35:05:01; C*07:03; DQB1*03:03). The two first fields identify the protein differences.

To find out more about allele nomenclature and understand the meaning of each group of digits see: http://hla.alleles.org/nomenclature/naming.html

What is the physiological role of HLA molecules?

Antigen presentation by HLA-II

After being split into peptides by proteases, extracellular antigens (e.g., bacteria) are presented by dendritic cells on HLA-II molecules. These molecules, expressed only on presenting cells, are formed by two beta and alpha chains that have a groove or slot (peptide groove) into which the peptides are inserted.

Bacterial peptides have between 13 and 24 peptides. The [HLA-II + peptide] complex becomes expressed in the membrane of the host cell (APC). In the membrane, the [HLA-II + peptide] complex is recognized by the specific T cell receptor (TCR) of CD4 + T lymphocytes.

Antigen presentation by HLA-I

Intracellular antigens (e.g., virus) are degraded in the proteasome, in peptides generally 8-10 amino acids long. These peptides are driven into the endoplasmic reticulum for binding proteins (TAP1-TAP2). Here, peptides bind to the peptide groove of HLA class I molecules (HLA-I). The [HLA-I + peptide] complex is expressed in the membrane, where it is recognized by lymphocytes that have the specific TCR of CD8 + T lymphocytes for that particular [HLA-I + peptide] complex.

A proliferation of specific clones occurs, and its ability to exert direct CTL cytotoxicity on target cells infected by virus, and only on the infected ones, is due to the fine specificity of TCR for the complex HLA-I + peptide.

How does allogeneic response develop?

Allogeneic response uses the same mechanisms as the immune response (IR) mounted against "dangerous agents" like microbes, except that human organs do not present the "pathogen-associated molecules" (LPS, double chain, RNA) which usually trigger "alarm systems" such as dendritic cell activation.

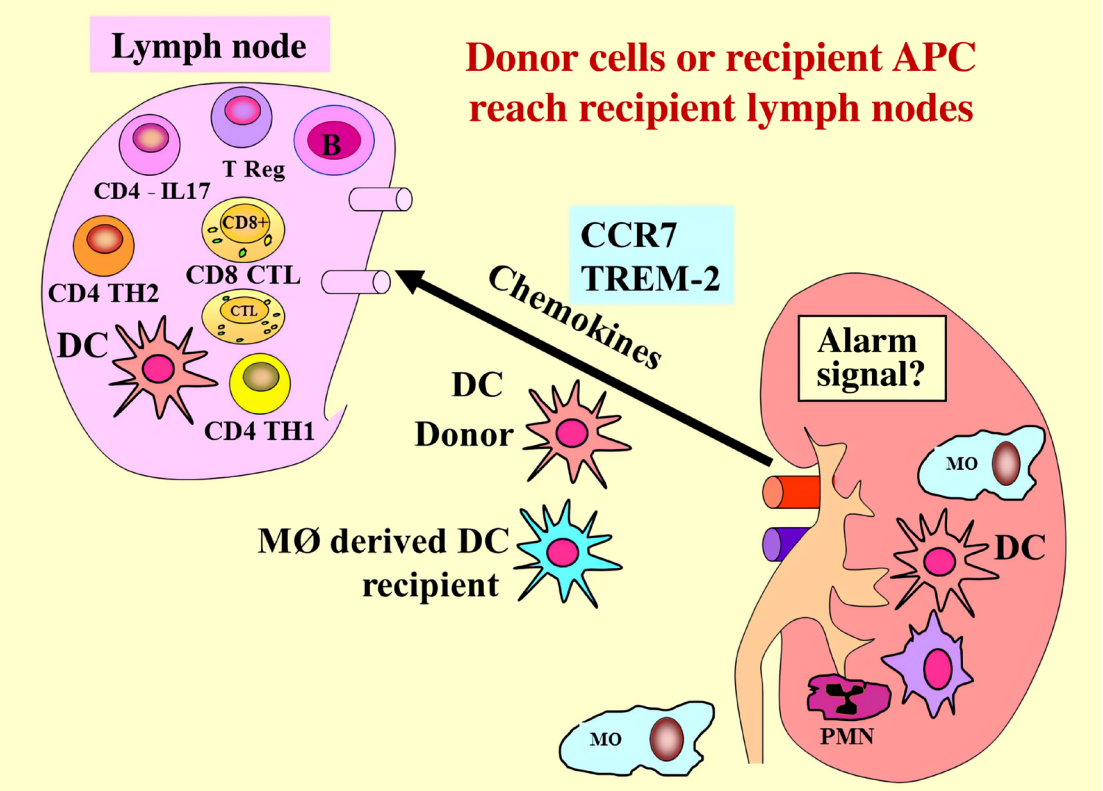

Figure 3. Donor cells or recipient APC cells reach recipient lymph nodes.

Initially, a migration of donor cells is produced to the lymph node of the receptor, which are either 1) Donor passenger dendritic cells, acting as antigen presenting cells (APC), or 2) Recipient APC that have processed donor cells. The activation of T cells takes place in the lymph node, where alloantigens are recognized as "foreign" through direct or indirect recognition.

How does the immune system recognize alloantigens?

Alloantigens can be recognized by several different mechanisms.

Direct recognition

Donor HLA molecules can be recognized directly by the recipient T cells on the graft cells, presenting endothelial or graft endothelial cells. This does not require antigen processing. Memory T cells against previous viral infections can recognize donor HLA by direct recognition.

In these circumstances, it could be said that the recipient mistakenly considers the donor HLA molecule with its own HLA molecule, presenting a foreign peptide. This direct mechanism determines that the number of T cells able to recognize the graft as foreign is significantly greater than for other external antigens [1].

Therefore, the "alarm signals" required to trigger a primary response are not necessary. Fortunately, the capacity of donor cells with antigen-presenting cells reduces in frequency over time, having more importance during the first year. This mechanism is related to acute cellular rejection in sensitized patients.

Indirect recognition

Donor HLA molecules can also be processed by recipient APC cells, as usually happens with foreign antigens. These cells fractionate peptides and present them as peptides within the context of recipient HLA. Both professional dendritic cells and, usually, the HLA mechanism persist throughout the life of the graft and are possibly responsible for maintenance of anti-HLA antibody production.

More recently, a newly described possibility is the direct incorporation of complete donor HLA molecules into the membrane of professional recipient APCs. This additional mechanism has been called cross-presentation.

The role of natural killer (NK) cells is another mechanism currently under study. NK cells have killer inhibitory receptors (KIRs) that control the correct expression of HLA in target cells, killing cells without the correct inhibitory signal. These receptors recognize polymorphic sequences on the HLA-C, B or A molecules. The absence of the alleles providing the inhibitory signal in the donor cells can play an unknown role in rejection.

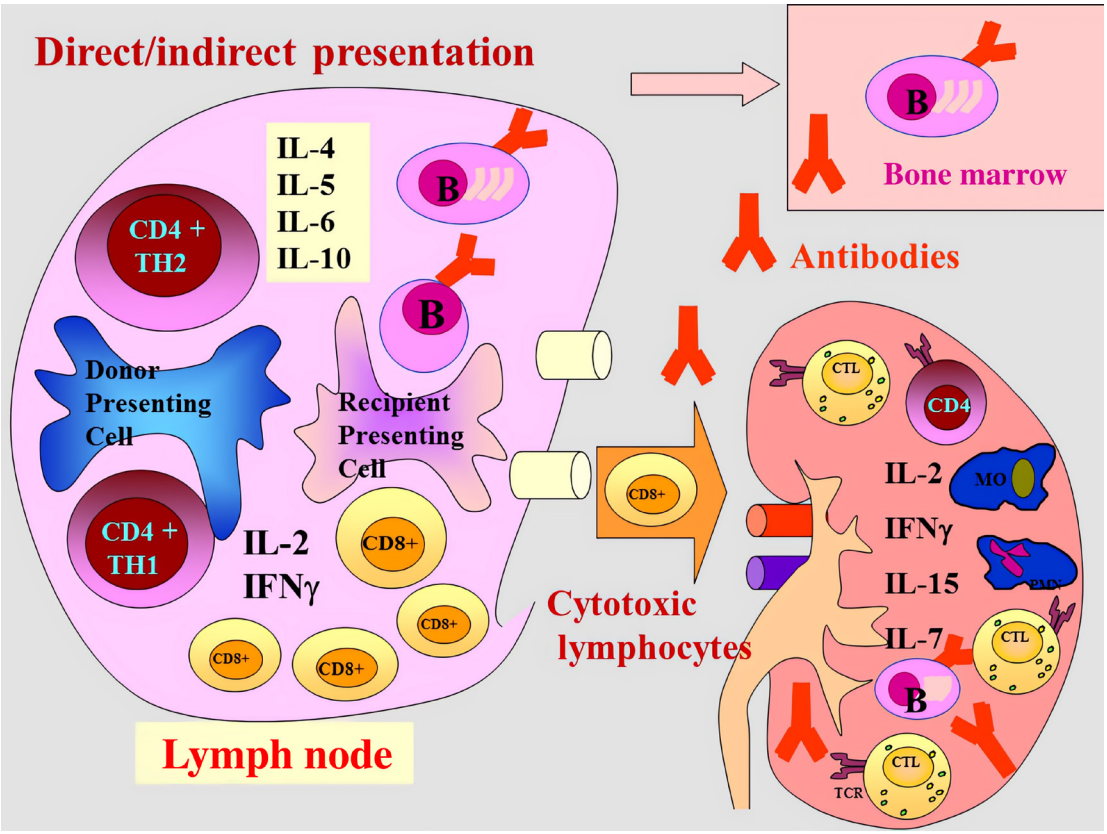

Figure 4. Direct indirect presentation.

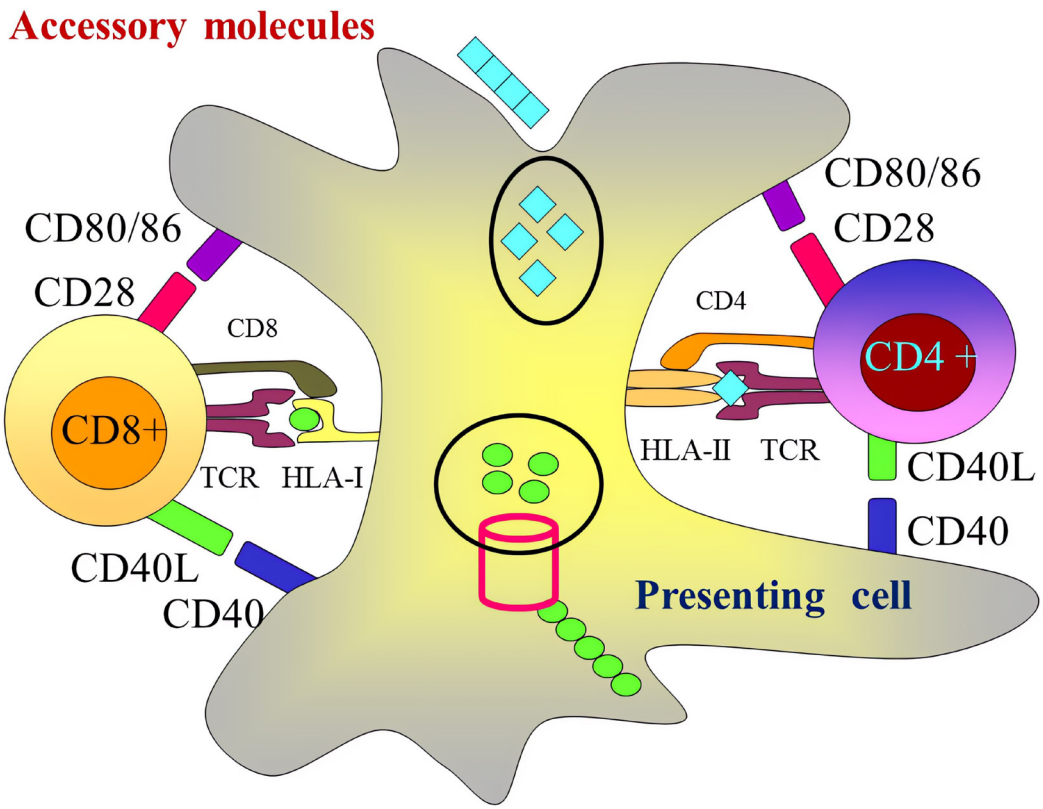

Figure 5. Accessory molecules.

2. ALLOGENEIC RESPONSE

T cell response to antigens and antigen-presenting cells (APC)

T cell response is activated when T cells expressing a specific TCR are able to interact with HLA molecules charged with "foreign peptide".

However, for complete T cell activation some additional signals are required.

APCs are recognized by T cells possessing the appropriate TCR, and are able to provide some additional signals to the T cell:

1. Antigen-specific signal: by interaction of specific TCR with the HLA.
2. Costimulatory or accessory signals: by interaction of CD80 or CD86 on antigen-presenting cells with CD28 or CTLA4 on recipient T cells. Other costimulatory signals are CD40-CD40L, CD4-HLA-II, CD8-HLA-I.

The set of two signals triggers activation of several transcription factors, including NFAT. These factors, by binding to the regulatory region of the IL-2 gene, are able to activate IL-2 mRNA production that will be then translated to the IL-2 protein as well as other cytokines (or interleukins) inducing the activation of T cell subsets.

In conjunction with the expression of receptors for IL-2 (IL-2R), the secreted IL-2 induces the signal necessary to initiate cell replication, which is essential for the immune response to be truly effective. This is the clonal expansion of specific T cells.

Table 3. Cells involved in rejection

Cell types	Function	Result
CD4+TH1	IL-2, IFN-gamma, TNF-alpha	Inflammation and clonal expansion
CD4+TH2	IL-4, IL-5, IL-6, IL-10, IL-13	Collaboration and differentiation of B cells
Cytotoxic T lymphocytes	Specific cytotoxicity (CTL)	Lysis and apoptosis of allogeneic cells
B Lymphocytes	Antibody production	Activation of Cs and endothelium destruction
NK cells	Natural cytotoxicity	Apoptosis of allogeneic cells
Macrophages	IL-1, ADCC	Inflammation, fibroblast activation
Tregs, CD4+CD25hiFOXP3+	Inhibits proliferation of T and B cells	Reduction of alloreactive effector T cells
Bregs, transitional CD19+CD24hiCD38hi	IL-10	Suppression of DC maturation and T cells

How do responder cells accumulate in the graft?

To reach the graft recipient, activated cells free from the lymph nodes travel to the graft oriented by chemokines. The endothelia retain these cells with the complementary adhesion molecules present on lymphocytes and the endothelium.

The expression and activation of adhesion molecules on the endothelium occurs because of activation by interleukins, in particular TNF alpha and IFN gamma, produced by the monocytes and lymphocytes themselves.

The adhesion molecules involved are mainly E-selectin and ICAM1, V-CAM (CD54) induced in the endothelium, Sialyl-LewisX, VLA4, LFA1 (CD11a-CD18) in lymphocytes, and possibly CD31, which mediates trans-endothelial migration.

Chemokines are chemotactic proteins which control the attraction of neutrophils, macrophages, T cells and NK cells to territories.

Chemokines play a role in different processes related to the transplant:

1. The accumulation of neutrophils during reperfusion and during the first 48 hours posttransplant.
2. Allowing antigen-specific response and facilitating graft infiltration by T cells, macrophages and NK cells from day 5.
3. Chronic graft rejection, by facilitating macrophage infiltration.

In transplantation, the most important chemokines seem to be: CCR3, CXCR5 and IP-10/CXCL10 that, when inhibited, block lymphocyte infiltration and increase allograft survival. Another two, CCR7 and TREM-2, participate in the migration of lymphocytes to lymph nodes, and S1PR1-S1P participates in the homing of lymphocytes in lymph nodes.

It is important to remember that CTL and antibodies are antigen-specific whereas cytokine, chemokine and adhesion molecule expression is not antigen-specific. The production of CTL in an inflammatory area can produce effects in lymphocytes carrying the adequate cytokine receptor.

Although there are many cell types and elements involved in alloresponse, effectors are those with the capacity to distinguish donor cells from recipient cells, principally by means of two mechanisms:

4. Cytotoxic T lymphocytes (CTL): cellular rejection.
5. Antibodies: humoral rejection.

The third mechanism, NK cells, has been poorly studied in organ transplantation, although the high expression of NK-related genes in antibody-mediated rejection (ABMR) may indicate a special role for antibody-dependent cellular cytotoxicity (ADCC).

Cytotoxic T lymphocytes (CTL)

These are principally CD8+.

Direct cytotoxic activity is mediated by two mechanisms:

6. Perforin secretion of the target cell membrane allowing the passage of “granzyme”, an apoptosis-inducing protein.
7. Interaction between FAS (CD95) and FAS-L (CD95L) that induces DNA fragmentation (or apoptosis) in the target cell.

Before the introduction of immunosuppressants like calcineurin inhibitors, the most frequent problem was cellular response.

Anti-HLA antibodies

Alloantibodies are currently the main effector of rejection. They act using different mechanisms:

Complement activation

1. Cell lysis through C56789 attack complex;
2. Opsonization by C3b; and
3. Attracting polymorphonuclear cells: C3a and C5a-mediated.

Antibody-dependent cellular cytotoxicity (ADCC)

In presence of antibodies, cells with receptors for the Fc for immunoglobulins may be used as recognition elements, causing the lysis of target cells by a mechanism independent of complement, using the same mechanisms as CTL though granzyme and perforin liberation.

Direct Activation of endothelium

It seems that the binding of antibodies to HLA can produce, by itself, the induction of endothelium proliferation that can be important in some kinds of chronic dysfunction.

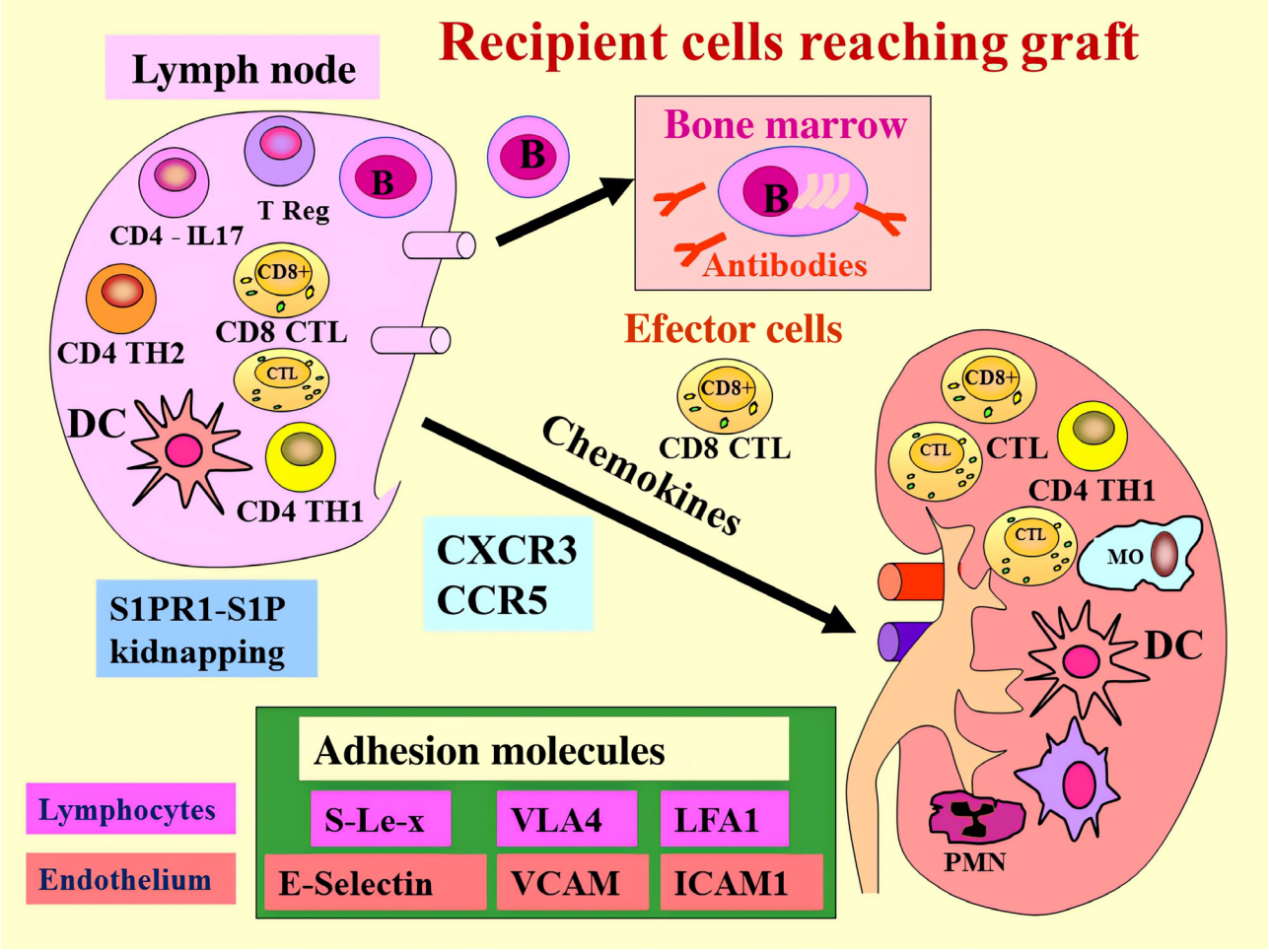

Figure 6. Recipient cells reach graft.

Are there different types of rejection?

Hyperacute rejection

This is currently an infrequent finding because there are now different ways to prevent it before transplantation. Hyperacute rejection occurs during the first 24 to 48 hours, sometimes within minutes of reperfusion. The organ becomes cyanotic and oedematous.

Characterized by:

- Deposits of antibodies and complement that destroy the graft endothelium.
- Great polymorphonuclear cell infiltration with sparse lymphocytic infiltrate.
- Platelet thrombus that obstructs blood flow.

Incidence of rejection is dramatically reduced by the exclusion, before transplantation, of potential recipients with antibodies against donor HLA antigens using crossmatching.

There are currently 3 different techniques to perform crossmatching: cytotoxicity, flow cytometry, and virtual crossmatch.

If crossmatching is negative, the incidence of hyperacute rejection is less than 2%.

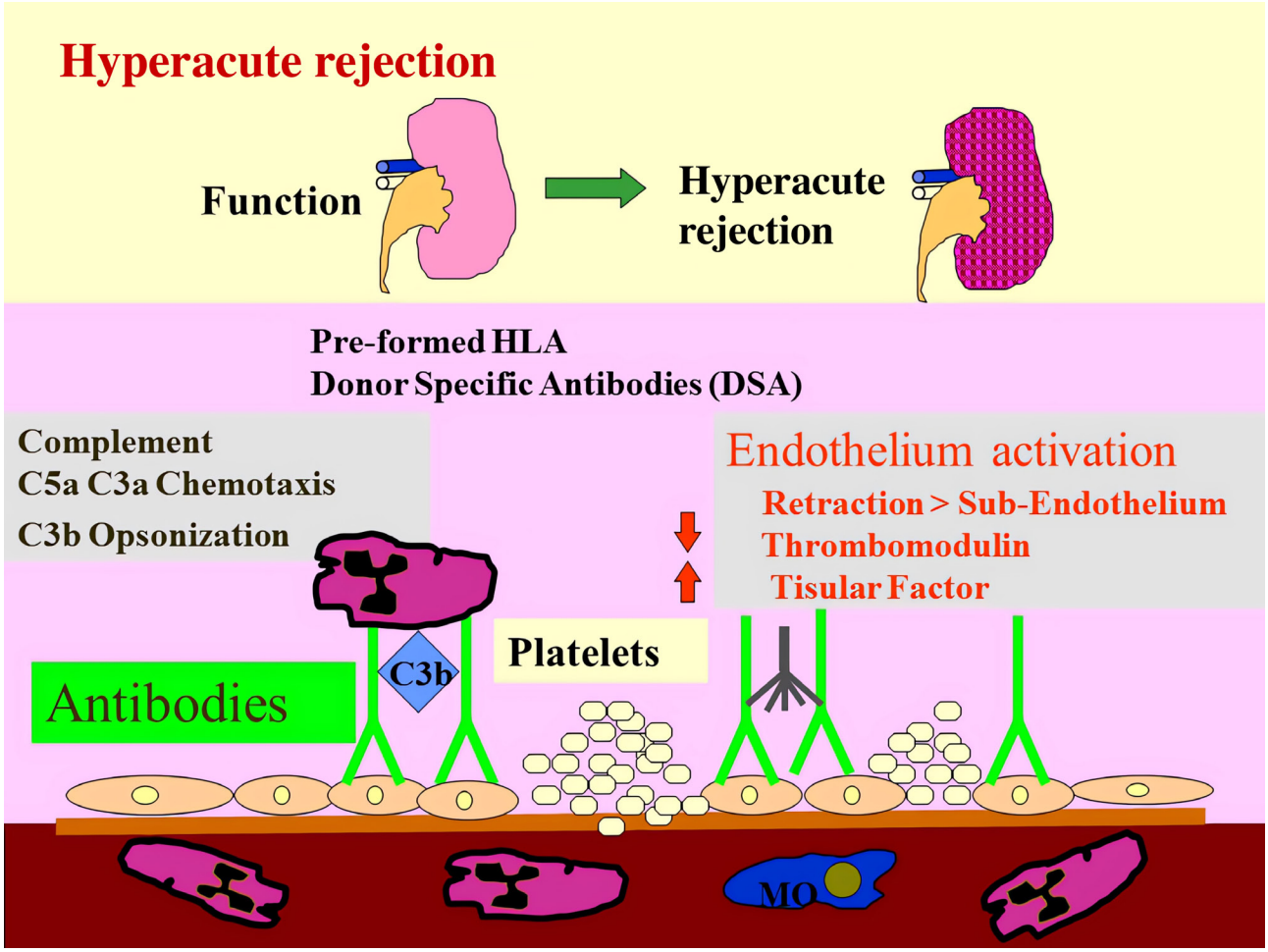

Figure 7. Hyperacute rejection.

Acute cellular rejection

This generally occurs during the first year of the graft.

It is characterized by a mononuclear cell infiltrate: CD8+ T lymphocytes, CD4+ T lymphocytes, B lymphocytes and macrophages. Occasionally there may be some polymorphonuclear cells, eosinophils and basophils.

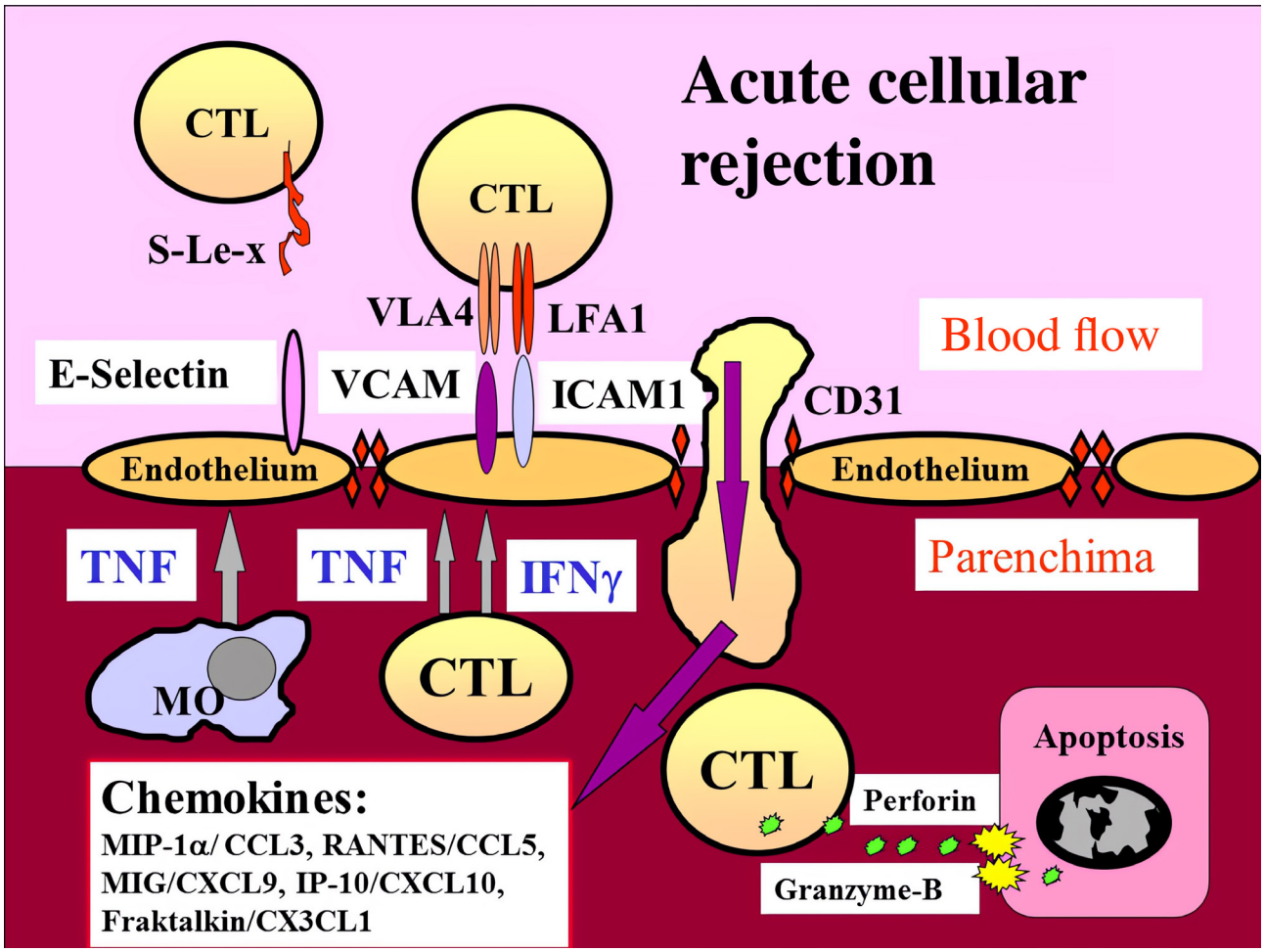

Figure 8. Acute cellular rejection.

Acute humoral rejection (or vascular rejection)

This is characterized by the predominance of endothelium destruction with signs of vasculitis, and polymorphonuclear infiltrate of capillaries.

It is frequently, but not always, associated with C4d deposition, and depending on the timeline of detection, C4d is a complement component that, after activation, fixes to the tissues and remains there for some time. It is a consequence of the appearance of *de novo* donor-specific alloantibodies (DSA).

Both cellular and humoral rejection often coexist. Cellular rejection is more sensitive to immunosuppressive therapy treatment with corticoid bolus, whereas vascular rejection is more frequently corticoid resistant.

Cellular rejection depends on the constant production of CTL cells, and this is why it is more sensitive to classical immunosuppressant drugs. Conversely, once triggered, the induced plasma cells are less sensitive to classical immunosuppressants, and antibody-removal treatment is necessary.

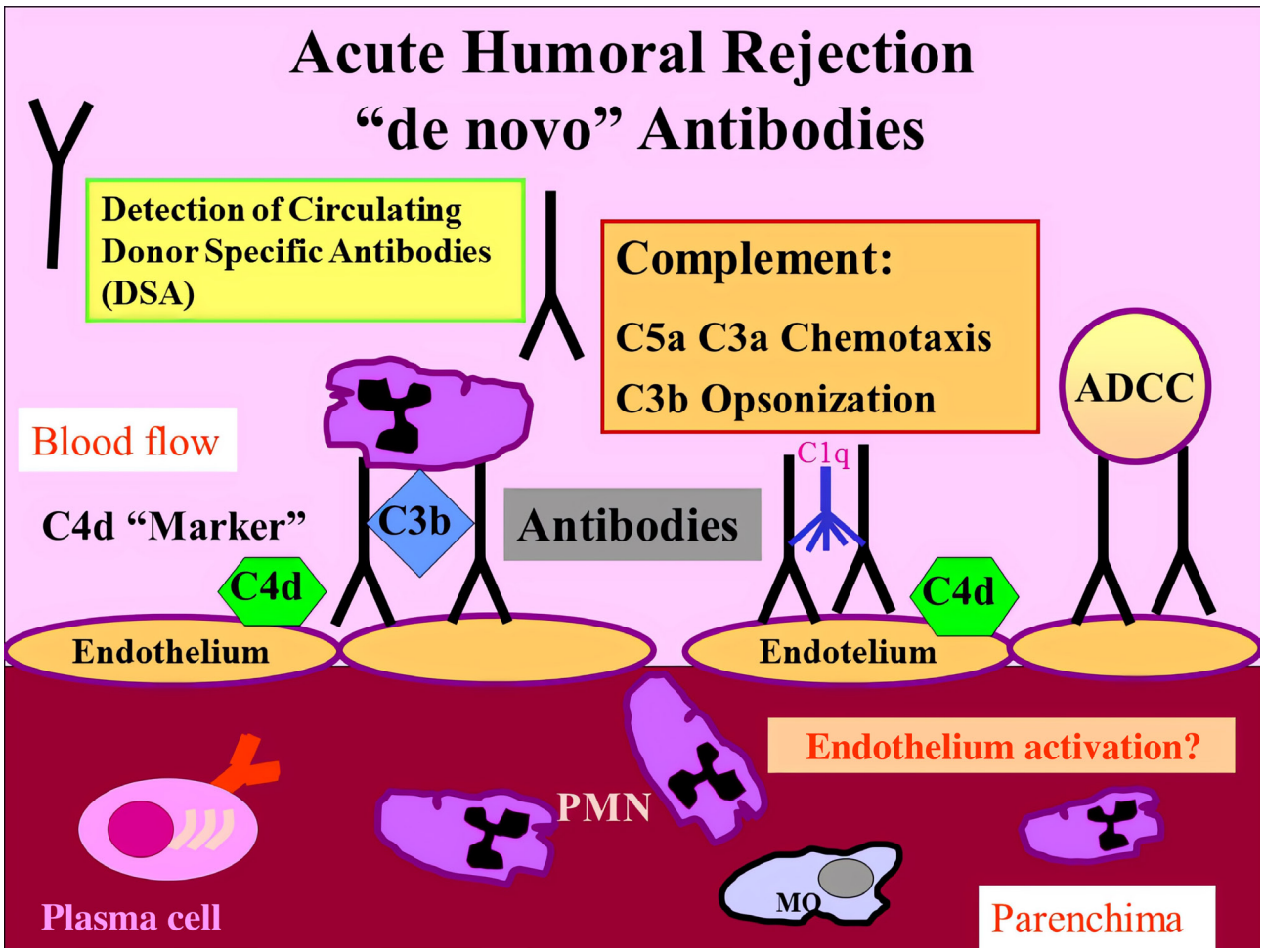

Figure 9. Acute humoral rejection.

Chronic rejection

Chronic graft disease: This is a late-onset process that can occur years after transplantation and may be accompanied by an obliterative proliferation of vascular walls, glomerular atrophy and/or interstitial fibrosis. It has different pathogenic mechanisms.

The literature increasingly associates the appearance of chronic rejection with the presence of anti-HLA alloantibodies in the patient, induced *de novo* by the graft in posttransplant, although the clinical damage may occur months or years later than DSA detection. *De novo* DSA have an important role in the obliterative proliferation of vascular walls, presumably through the multifactorial expression of a vessel defensive response to the presence of repeated micro-injuries.

3. ANTIBODIES AND GRAFT SURVIVAL

How can we prevent humoral organ rejection?

With the use of modern immunosuppression (see information about immunosuppression below), cellular rejection is better-controlled, and its incidence has been greatly reduced. However, immunosuppression is less effective in the antibody-mediated rejection produced by *de novo* posttransplant alloantibodies, and not effective at all in hyperacute rejection.

One of the few effective strategies to avoid the hyperacute rejection caused by preformed antibodies is to monitor and identify acceptable incompatibilities before transplantation, namely by identifying donor organs with HLA antigens against which the recipient has no antibodies.

For this reason, patients on the waiting list for a transplant have to be monitored for anti-HLA antibodies and the reacting specificities of these antibodies must be identified. In addition, a final test must be performed between recipient sera and donor cells to confirm that recipient antibodies do not react with donor HLA alleles.

This final test is the crossmatch. There are several techniques to screen and identify both sera specificities and crossmatching. The techniques have different sensitivities and positive predictive values, the correct use and interpretation of which are important for graft survival.

Alloantibody determination techniques

Panel-reactive antibody determination technique

This technique, PRA, detects the presence of complement activation (cytotoxic) antibodies in serum, particularly IgG1, IgG3, and IgM. The results are informed as a percentage and specificity:

» Percentage: Indicates the probability of a positive crossmatch by cytotoxicity with random donors.

» Specificity: Indicates the high probability of a positive CDC crossmatch with a donor possessing this HLA allele.

Solid phase screening

Uses surfaces, principally polystyrene beads coated with purified molecules of HLA-I (HLA-A, B, C) or HLA-II (DR, DQ, DP) from several donors.

Reactive antibodies are normally identified with a fluorescent-labelled secondary anti-IgG antibody, and the intensity of the fluorescence is read with a dedicated instrument (Luminex ®).

The screening of alloantibodies by anti-HLA solid phase (IgG) (Luminex ®):

» Has greater sensitivity than PRA cytotoxicity (CDC).

» No IgM antibodies are detected unless specific IgM secondary antibodies were used.

Solid phase single antigen test:

Uses beads coated with purified molecules of HLA-I (HLA-A, B, C) or HLA-II (DR, DQ, DP) with only one allele per bead. The specificity of the antibodies is identified with a secondary fluorescent-labelled anti-IgG antibody.

» This technique closely defines the acceptable incompatibilities, in other words, HLA alleles against which a transplant candidate has no antibodies.

» Knowledge of the acceptable incompatibilities and donor candidate HLA typing can define what is known as the virtual crossmatch for the locus whose typing becomes available.

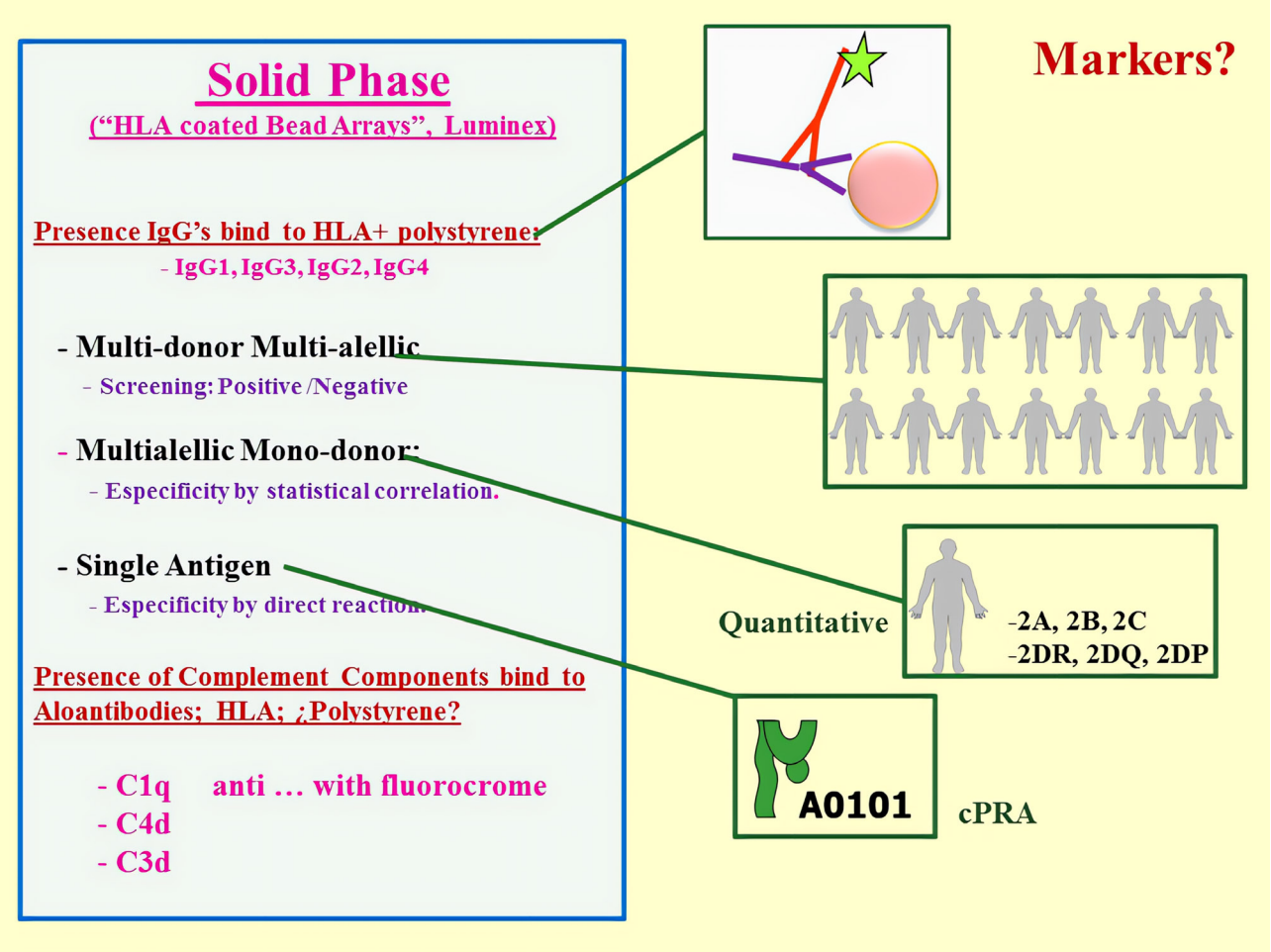

Figure 10. Solid phase.

Crossmatching techniques

Complement-dependent cytotoxicity crossmatch (CDC-XM):

This technique is based on the binding of recipient's antibodies to donor cell surface lymphocytes. If these specific antibodies are able to activate complement, the complement membrane attack complex (MAC) damages the cell membrane allowing vital colorants to enter the cell. If positive, it contraindicates the transplantation of kidney, heart or lung, but not liver. In kidney transplants, a positive CDC-XM has a predictive value for hyperacute rejection of over 70%.

It is possible to perform CDC-XM with isolated T and B cells.

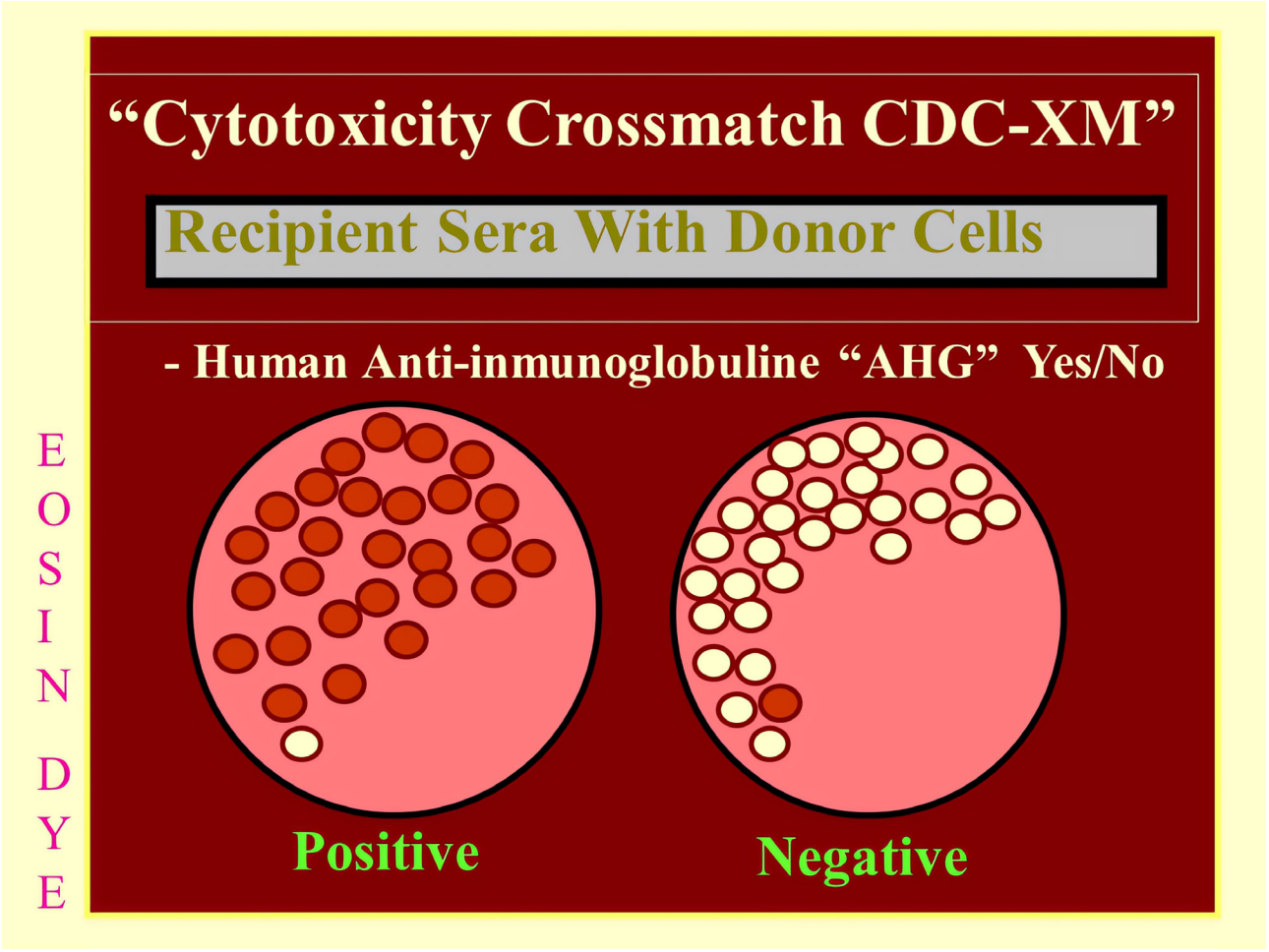

Figure 11. Cytotoxicity crossmatch CDC-XM.

Lymphocyte crossmatch by flow cytometry (FC-XM)

Detects recipient IgG binding to donor cells. It detects both cytotoxic and non-cytotoxic IgG, using MoAb to identify T-cell (anti-CD3) and B-cell (anti-CD19) markers, it is possible to distinguish anti-HLA-I antibodies (positives for T and B cells) from anti-HLA-II antibodies (positive only for B cells).

To assess cytometry crossmatch positivity and negativity, we use the shift in median channel fluorescence, SMCF. This is the result of subtracting the median channel fluorescence of the negative control from the median channel fluorescence of the serum. It also provides a semi-quantitative rating that gives an approximate notion of the quantity of anti-donor HLA antibodies.

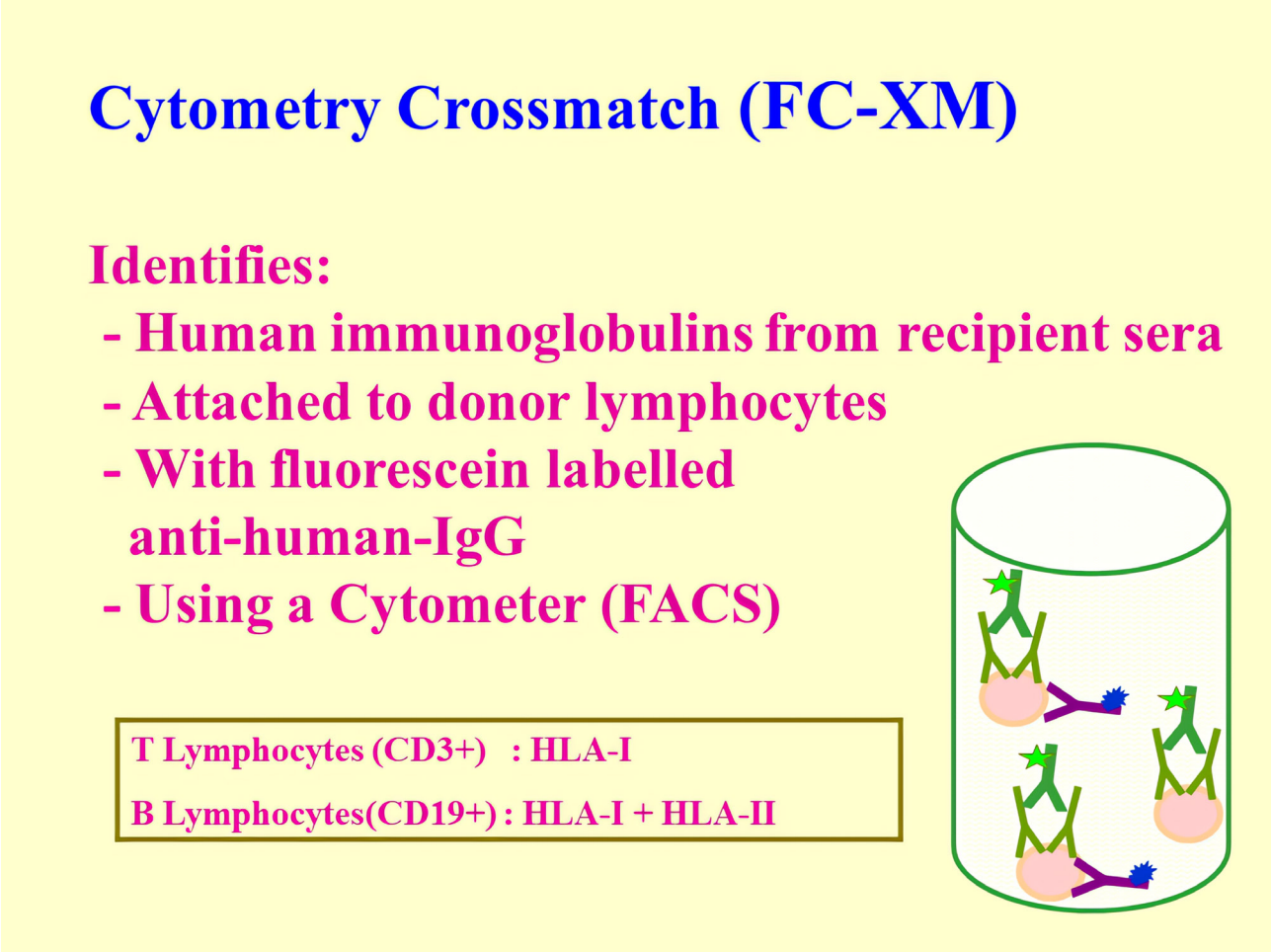

Figure 12. Cytometry crossmatch.

Sample needed for crossmatching

Although this can depend on the rules of each laboratory, in general, it is necessary to have sera from the recipient (clotted blood) and lymphocytes from the donor. In living donors, lymphocytes are obtained from peripheral blood: preferentially defibrinated or with EDTA. In cadaveric donors, lymphocytes from lymph-nodes are preferable but lymphocytes from the spleen or peripheral blood can be acceptable. DNA typing usually requires EDTA blood.that gives an approximate notion of the quantity of anti-donor HLA antibodies.

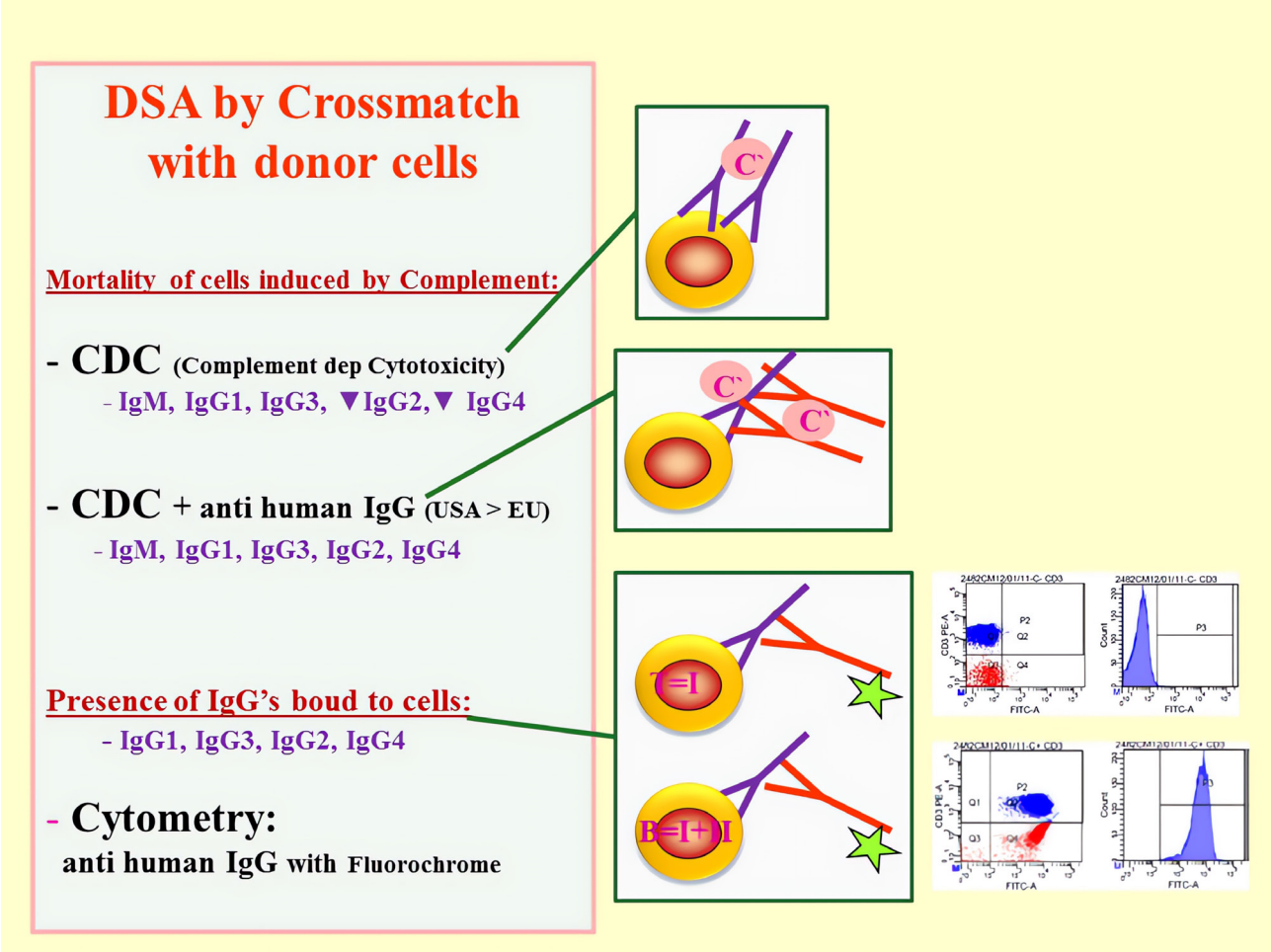

Figure 13. DSA by crossmatch with donor cells.

Virtual crossmatch (V-XM)

V-XM is a prediction of the real crossmatch, which can be performed knowing the alleles present in the donor and the Ab specificities in the recipient sera, identified using the single antigen bead test (SAB).

An absence of reactivity with the donor alleles is considered V-XM negative. It is highly specific and, for this reason, provides a good prediction of negative crossmatch. However, if it is positive, the positive predictive value for hyperacute rejection is much lower than the "real" crossmatch by cytotoxicity or cytometry. If the virtual crossmatch is the only positive result, this indicates a higher risk of acute antibody-mediated rejection episodes, but not necessarily a graft loss.

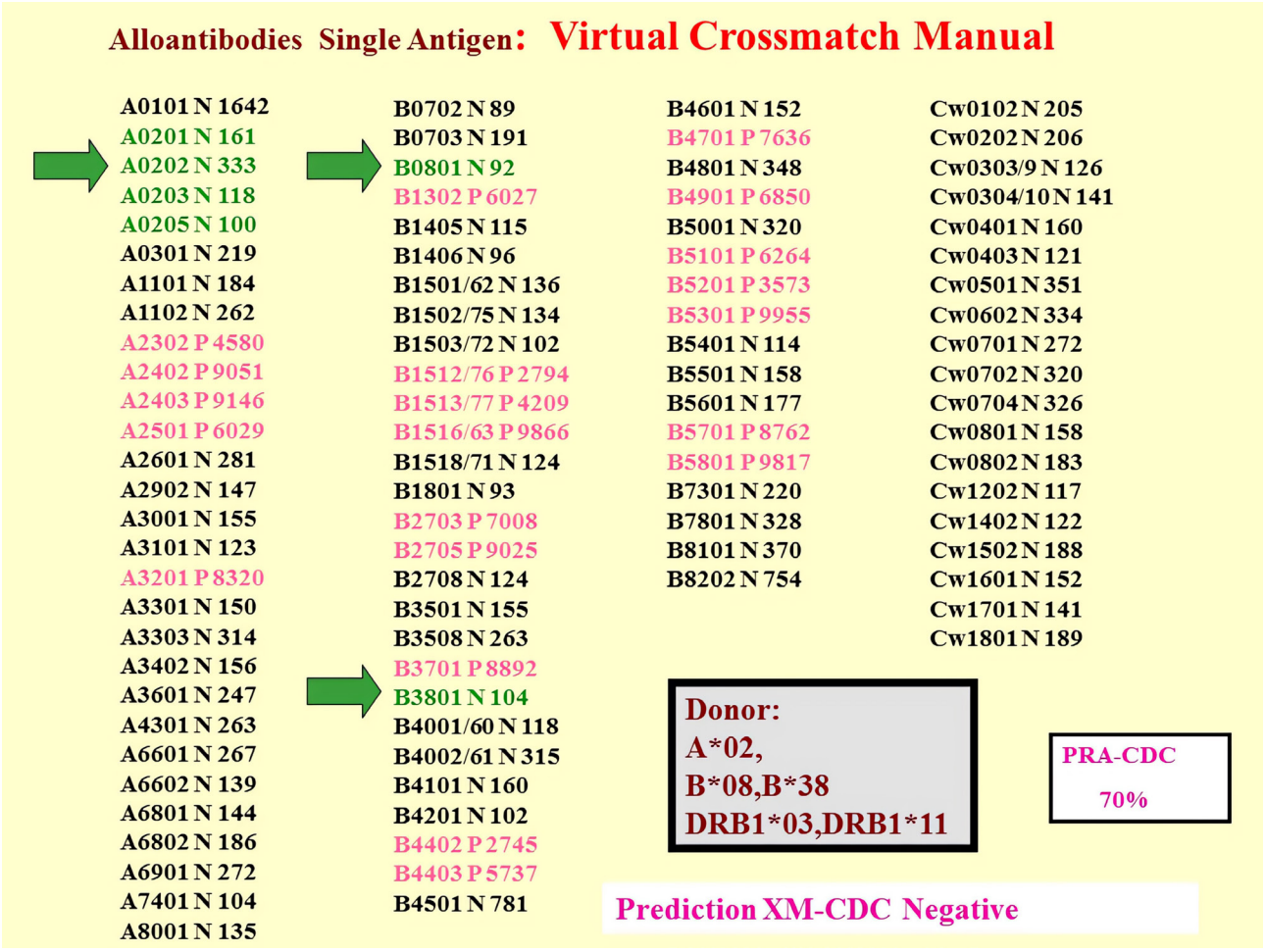

Figure 14. Virtual crossmatch manual.

Non-HLA antibodies

There are other polymorphic molecules that can also induce alloantibodies, the best known of which is MICA, a protein expressed only on activated endothelial cells codified in the same chromosome region as HLA genes. Antibodies against GSTT1 had also been described as targets for rejection, especially in the liver.

Table 4. Tests used and the reason for using them

Test	Reason used
Panel-reactive antibody (PRA) screening	
Cytotoxicity (CDC)	Best predictor of the risk of CDC-XM positivity
Solid phase (SP)	Most sensitive (rules out auto-Ab)
Specificity assignment in panel-reactive antibodies (PRA)	
Cytotoxicity (CDC)	Predicts CDC-XM positivity low PRA
Single antigen (SPSA)	Predicts negative CDC and FC XM
Even highly sensitized (virtual XM)	
Crossmatch (XM)	
Cytotoxicity (CDC)	Highest positive predictive value for hyper-acute rejection
Flow cytometry (FC)	Most sensitive using real donor cells
Predicts higher risk of graft loss in Re-Tx	
Virtual	Bead arrays identifies more specifities any other test
Useful to exclude DSA depending on cut-off	
Predicts higher risk of ABMR	

Table 5. Interpretation of different crossmatching techniques

Cytotoxicity (CDC)	Cytometry	Virtual crossmatch	Prognostic value
Positive	Positive	Positive	80% risk of hyperacute rejection 48 h
Positive	Negative	Negative	May be auto-antibodies (lgM) No risk: Recent sensitization must be excluded
Negative	Positive	Positive	Risk of graft loss at 1 year - First transplant: 10% - Retransplant: 30%
Negative	Negative	Positive	Risk of antibody-mediated rejections from 5% to 55% in 1st year

Transplanting highly sensitized patients

The currently most common method for measuring level of sensitization is calculated panel-reactive antibody (CPRA). This is a calculation of the percentage of donors who would be positive in the virtual crossmatch. According to this value, patients are classified as non-sensitized (CPRA=0) or sensitized (CPRA between 0 and a value varying between 85% and 98%) in accordance with different organizations. Patients with a CPRA above these values are considered highly sensitized. For such patients, the best way to find an acceptable donor is to search for one who only has acceptable alleles in the largest possible donor pool.

Desensitization is only an alternative for a limited number of patients with a low titre of alloantibodies and is usually accomplished using a combination of plasma exchange, IVIG and anti-CD20 antibodies.

4. CONCEPTUAL BASIS OF IMMUNOSUPRESSION

How can we intervene in immune system response against the allograft?

Antigen-specific responsiveness depends on the clonal expansion of lymphocytes; clonal expansion is mediated by autocrine factors (cytokines) and requires DNA duplication.

- One of the most representative cytokines is IL-2. IL-2 secreted CD4+ TH1 cells are essential for expanding CTL, CD8+ and CD4+ helper cells.
- Other cytokines such as IL-6, IL-4, IL-10 are secreted by CD4 Th2 cells and participate in B cell differentiation, the production of antibodies and also the clonal expansion of T and B cells.

Another determining factor in immune response is relocation of the activated lymphocytes in the graft. Lymphocytes must leave the lymph node, detect capillaries expressing adhesion molecules and migrate through the endothelium into the parenchyma following attracting chemokines.

The ideal immunosuppressant must:

- Avoid the clonal expansion of Ag-specific lymphocytes without affecting other cells (e.g., PMN cells).
- Block characteristic processes of lymphocytes, but not other cells.

Table 6. How do immunosuppressants block clonal expansion?

Mechanism	Immunosuppressant
Blocking transmission of the core TCR specific signal	Calcineurin Inhibitors
Blocking transmission of the signal produced by interaction between the receptor and interleukins (IL-2 and IL-2R)	mTOR inhibitors (Rapamycin)
Blocking DNA replication	Mycophenolate mofetil (MMF)
Interfering the CD28 accessory signal	CTLA4lg fusion protein
Interfering the CD40 accessory signal	Anti CD154 monoclonal antibodies
By destruction of almost all lymphocytes	ATG, ALG, lymphoid irradiation Anti-CD3 monoclonal antibodies
Destruction (or blocking) activated lymphocytes	Anti-CD-25 monoclonal antibodies
Acting on signal of T cell expansion	Corticosteroids

Table 7. How do immunosuppressants block lymphocyte relocation?

Mechanism	Immunosuppressant
Blocking interleukin (TNF alpha and IFN gamma) that induce adhesion molecules such as E-selectin, V-CAM, ICAM1	Calcineurin Inhibitors
Inhibiting signals which determine the trans-endothelial migration of lymphocytes	Blockers of chemokines or their receptors
Acting on inflammation and recirculation	Corticosteroids

Calcineurin inhibitors: cyclosporine and tacrolimus

The gene encoding IL-2 as well as other interleukins is transcribed into mRNA and translated into protein when the transcription factors bind to the regulatory region. This requires some factors, such as NFAT, to migrate from the cytoplasm to the nucleus. The NFAT migrates to the nucleus where it is dephosphorylated by calcineurin, a phosphatase.

The phosphatase activity of calcineurin is inhibited by the cyclosporine + cyclophilin complex, and by the tacrolimus + FKBP complex. Both cyclophilin and FKBP are cytoplasmic proteins. This blocking system has a high specificity for T lymphocyte.

Table 8. Effect of calcineurin inhibitors on the secretion of interleukins

Interleukin	Interleukin	Cell	Interleukin	Interleukin	Cell
IL-1	©	M↓	IL-8	φ↓	T
IL-2	↓↓↓	T	IL-10	↓	T
IL-3	↓↓↓	T	GM-CSF	↓↓↓	T
IL-4	↓↓↓	T	IFN-↓	γ↓↓	T
IL-5	↓↓↓	T	TNF-↓	α↓↓	T
IL-6	↓↓↓	Mast	TGF-↓	β↑↑	T

mTOR inhibitors: rapamycin, sirolimus, everolimus

These inhibitors also bind to FKBP, but their effect does not act on calcineurin. By binding to rapamycin, FKBP sequesters mTOR protein.

- mTOR is a protein necessary for transmitting the signal provided by the IL2-IL2R binding.
- The abduction of mTOR prevents the IL-2-IL-2R signal reaching the nucleus and initiating DNA synthesis.

Mycophenolate mofetil

» Non-competitive inhibitor of IMPDH. Key enzyme in the *de novo* synthesis of purine.

» IMPDH inhibition decreases available GTP and inhibits DNA synthesis in lymphocytes.

» Lymphocytes are highly dependent on the *de novo* synthesis of purines.

Corticosteroids

Anti-inflammatory effect:

» Stabilize the membrane of lysosomes.

» Reduce chemotaxis and phagocytosis of macrophages and neutrophils.

» Inhibit the secretion of cytokines: IL-1.

» Inhibit the activity of transcription factors: Decreased expression of HLA-class-II from the APC. Produce depletion of CD4 lymphocytes by inhibiting lymphocyte recirculation.

Table 8. Effect of calcineurin inhibitors on the secretion of interleukins

Small-molecule drugs	Biological drugs	Drugs and interventions currently used for managing ABMR
Immunophilin-binding drugs (cyclophilin binding) CN inhibitors: cyclosporine – FKBP-binding CN inhibitor: tacrolimus mTOR inhibitors: sirolimus, everolimus Inhibitors of *de novo* purine or pyrimidine synthesis IMPDH inhibitors: MMF, MPA Antimetabolites Azathioprine	Depleting Polyclonal rabbit or horse anti-thymocyte globulin Non-depleting/partially depleting Belatacept/LEA29Y: CTLA4Ig fusion protein Basiliximab: chimeric monoclonal anti-CD25 (IL-2Ra)	Plasmapheresis IVIG: trials Rituximab: chimeric monoclonal anti-CD20; trials Eculizumab: humanized monoclonal anti-C5; trials - Bortezomib: proteasome inhibitor; trials

Abbreviations: ABMR, antibody-mediated rejection; CN, calcineurin; CTLA, cytotoxic T lymphocyte antigen; FKBP, FK506-binding protein; Ig, immunoglobulin; IMPDH, inosine monophosphate dehydrogenase; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin.

Modified from: Philip F Halloran et al.; 2014, Kidney International (2014) 85, 258 Antibody-mediated rejection, T cell–mediated rejection, and the injury-repair response: new insights from the Genome Canada studies of kidney transplant biopsies.

5. TOLERANCE INDUCTION

Is it possible to avoid the response to alloantigens and maintain response to infections?

Although immunosuppressive therapies have helped to dramatically reduce the incidence of acute graft rejection, longer-term results have not met expectations. The almost universal occurrence of graft fibrosis and patient death from cardiovascular disease or cancers are the main culprits for today modest results and, paradoxically, in all cases, the adverse effects of immunosuppressive treatment are major predisposing factors.

Thus, current thought is that the best way to prolong graft survival would be the safe elimination of immunosuppression by adapting the recipient's immune system to prevent response to donor alloantigens; in other words, inducing a state of donor-specific hyporesponsiveness or tolerance.

Proof of tolerance to an allograft has been shown experimentally in different animal models.

In humans, the clinical definition of tolerance is based on maintaining graft function without the need for chronic immunosuppressive therapy. The clinical outcomes of rejection and graft survival suggest that the liver is more susceptible to tolerance than other solid organs such as the kidney, heart or pancreas. This seems to be due to the different degrees of immunogenicity these organs generate, because of the different density of HLA molecule expression and the different ability of resident APC.

Operational tolerance manifests through the modulation of several simultaneous immunological processes:

- The frequency of precursor cellular effectors.
- The efficiency of antigen presentation.
- The activation threshold of effector cells.
- Regulation and alterations in the cell migration process.

For these reasons, a state of tolerance could potentially be achieved through several mechanisms.

One of the main barriers to overcome is the intrinsic nature of adaptive immunity. Thus, the phenomenon derived from heterologous immunity, i.e., cross-reacting to environmental antigens, may at any time evoke a response to alloantigens and, therefore, abort a state of donor-specific hyporesponsiveness.

Is it possible to identify operational tolerant patients?

Several collaborative studies have recently analysed the molecular characteristics that distinguish tolerant renal transplant patients and patients on chronic immunosuppressive therapy with stable graft function from patients with chronic immune rejection. These studies found an overexpression of B-cell-specific genes, as well as an increase in the B cell population, particularly the naïve B cell subpopulation, in peripheral blood. In addition, donor-specific cellular hyporesponse was detectable in the peripheral blood of most patients with tolerance.

This particular genetic signature in tolerant renal transplant recipients appears not to be the same as in liver transplant tolerant patients, among whom the genes associated with the natural killer subpopulation and iron metabolism appear to differentiate patients who reject the graft after the withdrawal of immunosuppression.

Multicentre, collaborative, prospective and randomized studies are being carried out that attempt to define operational tolerance biomarkers which allow discrimination of the patients on immunosuppressive therapy whose treatment can be removed or reduced as much as possible in an elective, secure way.

How can tolerance be induced?

Strategies to induce tolerance are based on diverting the balance between immune effector cells and immune regulatory cells in order to achieve a predominance of the latter. This objective can be achieved either by removing or suppressing effector cells or by inducing or transferring regulatory cells.

Thus, depletion of T cells using immunosuppressive drugs is an effective way to remove alloreactive effector cells. However, even if this treatment is able to prevent acute rejection, maintenance therapy is necessary to avoid the alloresponse induced by memory lymphocytes.

Some strategies have focused on attempting to facilitate cell anergy by blocking the second signal for T-cell activation and co-stimulation. As stated above, after antigen contact and in the absence of a co-stimulatory second signal, the T cell undergoes a process of anergy or apoptosis. Co-stimulatory molecule blockades comprising CD28 / CTLA4-CD80 / CD86 and CD40-CD40 ligands have been tested in experimental studies.

Other strategies acquiring increasing importance are based on endeavours to promote the expansion of regulatory T cells. These cells are mainly CD4+ CD25+ T cells that express the transcription factor FoxP3 and have a suppressive capacity of the donor-specific alloresponse. Relevant experimental studies show the adoptive transfer of this lymphocyte subpopulation may prevent the development of both acute rejection and chronic graft rejection.

To date, the most successful strategy to induce tolerance is the creation of allogeneic mixed chimeras by the administration of hematopoietic progenitors. Initially, clinical trials aimed to achieve complete chimerism through hematopoietic stem cell transplants with myeloablative conditioning to attain a total replacement of the recipient's hematopoietic system.

However, this approach is not acceptable for the majority of solid organ transplant candidates due to significant associated co-morbidity. Subsequent studies have found that mixed chimerism, reached when performing a non-myeloablative reduced intensity conditioning transplant, is sufficient to establish donor-specific tolerance through the induction of central deletion of alloreactive T and B lymphocytes.

Table 10. Potential biomarkers of tolerance in humans

Assay Type	Transplanted organ	Tissue assayed	Results in tolerance
Flow phenotyping			
B cells	Kidney	Blood	↑
NK cells	Liver (and kidney)	Blood	↑
γδ cells	Liver	Blood	↑
Plasmacytoid DC	Liver	Blood	↑
CD8+CD28- T cells	Kidney	Blood	↓
CD4+CD25hi T cells	Kidney and liver	Blood	↑
Gene expression			
B cell related genes	Kidney	Blood	↑
NK cell related genes	Liver	Blood	↑
γδ cells related genes	Liver	Blood	↑
FoxP3	Liver and kidney	Blood and graft	↑
CD20	Kidney	Urine	↑
TGFβ-regulated genes	Kidney	Blood	↑
Cellular assays			
MLR and CTL	Kidney	Blood	Hyporesponsive
Cytokine production	Kidney	Blood	Hyporesponsive
Trans-vivo DTH	Kidney	Blood	Hyporesponsive

Clinical transplantation tolerance [2]

CONCLUSIONS

- Understanding the functioning of the human immune system is essential in allograft transplantation.
- The different steps in allograft recognition, the build-up of immune response and the appropriate medication to suppress the system need to be known in order to understand the different therapies for different types of patients.
- Immunological risk and the role of the HLA system in rejection are important in order to provide the best possible protection for transplant patients.

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TOPIC 1 - Unit 2

Infections and malignancies

ORGAN TRANSPLANTATION

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INTRODUCTION

Overall survival rates have considerably improved in transplant patients over the years, mainly due to new immunosuppressive agents, but also thanks to the better management of short-term complications, which were historically associated with a poor outcome.

Nevertheless, longer life expectancy means more long-term complications such as cardiovascular disease and cancer.

Although cardiovascular disease is still the main cause of death in patients with a functioning graft, cancer may equal and even overtake this, particularly in older patients.

Apart from the higher incidence, cancers in transplant patients are more aggressive, have a less favourable prognosis and a worse response to treatment.

1. EPIDEMIOLOGY

Among patients who receive a cadaveric graft, the first-year risk of developing skin cancer is estimated to be over 30%. According to Kasiske et al. [1] the accumulated incidence of cancer (excluding non-melanocytic skin cancer) is: 1.2%, 1.9%, 3.3%, 5.5% and 7.5% at: 3, 6, 12, 24 and 36 months, respectively.

The cancer-induced mortality rate among transplant patients can be as high as 9-12%.

This makes the implementation of prevention measures, early diagnosis and treatment imperative in transplant patients.

There are three different oncogenic mechanisms.

1.1 Donor transmission of malignant disease

This has an extremely low frequency. According to the Spanish National Transplant Organization (NTO) consensus document, only 0.02% of transplant patients developed donor-transmitted cancer. Given the shortage of organs, different consensus accept donors with certain neoplastic diseases, i.e., low grade skin tumours or those with a low metastatic capacity (basal cell or squamous cell carcinoma), carcinomas *in situ*, low grade malignancy kidney tumours and certain central nervous system tumours (WHO grades 1 and 2; and in the absence of other risks factors, grade 3 as well).

Although there have been proposals for strategies to reduce tumour transmission risks, in practice it is not always possible to apply them. This may be due to the urgency in organ retrieval or the resources each country or donor hospital has, which may prevent the timely performance of recommended diagnostic testing and determinations, such as CT scans or biopsies with urgent anatomopathological examination. As a result, tumour diagnosis in a donor is sometimes made posttransplant.

When a transplant patient develops cancer, several options may be contemplated:

1. Tapering or withdrawal of immunosuppressive therapy.
2. Changing immunosuppressive agents (the CNIs may be switched to mTOR or proliferation signal inhibitors (sirolimus /everolimus because of their anti-tumoral activity).
3. Specific anti-tumoral treatment with chemotherapy, radiotherapy and/or surgery should be considered (including transplantectomy).

1.2 Recurrence of prior neoplasia in the recipient

The shorter the interval between the initial cancer in the recipient and the transplant, the higher the recurrence rate after the transplant. If the transplant candidate has a prior tumoral history, a certain waiting period is recommended between cancer remission and transplant. As we will see further on, this period varies according to tumour grade and type.

In this particular context, mTOR inhibitors may be chosen as an initial immunosuppression regimen so as to prevent tumour recurrence post-kidney transplant. Nevertheless, prospective studies are necessary to confirm the validity of this approach.

For patients on the waiting list with no history of malignancy, cancer screening is necessary, particularly in those over the age of 50.

1.3 *De novo* cancers

Apart from donor-transmitted cancers and the recurrence of prior neoplasms, transplant patients have a high risk of developing *de novo* cancers.

According to the ANZDATA register, the standardized relative risk for all neoplasia is 1.35 in dialysis patients compared to 3.27 in the transplant population. Furthermore, the global survival rate for patients with cancer is 2.2 years.

On comparing the different types of cancer between transplant patients and the general population, Kasiske et al. [1] noted non-melanocytic skin tumours. Kaposi sarcoma and non-Hodgkin lymphoma were at least 20 times more frequent than in the general population. Moreover, kidney cancers occurred 15 times more often, whereas those of bladder and testicles were only 3 times more common. Melanoma, leukaemia and hepatobiliary, cervical and vulvovaginal tumours were approximately 5 times more common and the rest of the most common cancers in the general population (colon, lung, prostate, stomach, oesophagus, ovary and breast) were twice higher in transplant patients.

Other authors state that kidney transplant patients have at least a 4 times higher risk of developing other neoplasms, including cancers of the oesophagus, liver, nasal cavity, vulva, vagina, cervix, penis, other male genital organs, bladder, thyroid and endocrinal glands.

Nevertheless, there are some cancers that only present a moderately higher risk than the general population, e.g., breast cancer stages 1 and 3 or colon carcinoma.

Therefore, the neoplasms that are most frequent among transplant patients are skin cancers (especially non-melanocytic ones), lymphomas, and lymphoproliferative diseases, which are considered as post-transplant lymphoproliferative disorder (PTLD).

Skin cancer, principally non-melanocytic tumours that represent approximately 90% of all skin neoplasms, is the most common cancer among kidney transplant patients. According to the Australian register, its overall incidence is 30% at 5 years and 82% at 20 years posttransplant.

However, incidence data vary according to the different studies conducted and registers. Thus, the Australia and New Zealand Dialysis and Transplant Registry, ANZDATA, showed a risk of over 30% at 10 years for developing skin cancer for cadaveric recipients. Another Australian study concluded that occurrence of skin cancer is directly related to the duration of immunosuppression. Thus, development of at least one non-melanocytic tumour occurs in 29.1, 52.2, 72.4 and 82.1% of cases when immunosuppression lasted <5, 5-10, 10-20 and >20 years respectively.

Among the transplant population, PTLDs represent an important class of neoplasm, with a relatively high incidence and high mortality. According to various authors, this occurs 10-29 times more often in transplant patients compared to the general population. For paediatric patients, incidence is different to the adult population. Thus, PTLD are the most common cancers and constitute 50% of all tumours, whereas skin cancer takes second place with an incidence rate of 20%.

Kaposi sarcoma is rare in the general population, but its incidence increases considerably in transplant patients, varying according to geographical location. Despite having an important skin component, it is normally categorized within “other cancers” since it can also affect organs like lungs, lymph nodes or the digestive system with a systemic nature.

2. RISK FACTORS

The most common posttransplant cancers are non-melanocytic skin cancer (2.6 times), melanoma (2.2 times), Kaposi sarcoma (9 times), non-Hodgkin lymphoma (3.3 times), mouth cancer (2.2 times) and kidney cancer (39% higher).

This suggests that immunosuppression, both its concentrations and duration, plays a key role in increasing risk.

Cancers with the greatest risk of onset (PTLD, Kaposi sarcoma, liver, oesophagus, cervix, vulva, vagina and penis) have in common the presence or suspicion of a viral component (oncovirus) in their aetiology, which would support the theory of an interaction between the immune system and oncoviruses in the aetiology of cancer. Despite acknowledging that immunosuppression is a key risk factor, other aspects should be considered: age at time of transplant, gender, and duration of the terminal kidney disease prior to transplant. In this respect, the ANZDATA register reports which analyse the risk factors associated with a higher incidence of cancer (excluding non-melanocytic skin cancers), show that gender and age at time of transplant in addition to the time lapse since transplantation are important prediction factors for the development of cancer.

The duration of terminal kidney disease prior to transplant is considered a risk factor for developing kidney cancer.

3. PATHOGENESIS

The main posttransplant oncogenic risk is directly related to immunosuppression and the main mechanisms are:

1. The direct action of certain immunosuppressor drugs (not linked to the immunosuppressor effect). There is data suggesting that both cyclosporine and tacrolimus might induce transforming growth factor beta 1 (TGF β1), associated with tumoral invasion and spread.
2. A sustained depression of the immune system which:
    1. Favours opportunist infections via virus with an oncogenic potential.
    2. Alters certain immune system components, such as the natural killer cells involved in immunological vigilance and the early elimination of neoplastic cells.

However, the chronic antigenic stimulation from transplanted organs and repetitive infections might stimulate a partially depressed immune system, favouring the development of lymphomas associated with transplants, a condition known as posttransplant lymphoproliferative disorder (PTLD).

4. TREATMENT OF CANCER PATIENTS ON THE WAITING LIST

All transplant candidates must be clinically assessed to rule out any undiagnosed neoplasms. Guidelines recommend that older patients on the waiting list for a longer time should be periodically assessed to detect any occult tumour.

The presence of any of the following is considered a contraindication for transplant:

1. An illness conditioning life expectancy to less than 2 years.
2. An active systemic infection.
3. Uncontrolled cancer despite treatment.

Metastasis, advanced breast or prostate cancer, and multiple myeloma contraindicate a transplant.

There are patients with a specific history of cancer that may be included on the waiting list. This decision should consider two essential factors:

1. The type of tumour, which determines the probability of recurrence.
2. The interval since diagnosis, treatment and/or surgery for the cancer, which is inversely proportional to the risk of recurrence after transplant.

For treated cancer patients who had undergone a transplant after less than a 2-year interval free of disease, the recurrence rate of the initial cancer had the highest incidence (54%).

On the other hand, recurrence capacity depends on type and stage. Thus, testicle or thyroid cancer generally have a low posttransplant recurrence rate (3-12% and 7-8%, respectively), whereas myeloma or nonmelanocytic skin cancer recur in a higher percentage of patients (67% and 48-62%, respectively). However, the same cancer type may behave differently depending on its stage of evolution on diagnosis. So, for breast cancer, the stage seems to be a determining factor for recurrence (5.4 and 8% in stages 1 and 2 and up to 63.6% in stage 3). In colonic cancer, Dukes' A or B1 stages present a 14% or 19% recurrence rate respectively, whereas most advanced stages of the same tumour will recur in up to 42% of cases. Taking into account these factors, we encounter tumours that require no waiting time, such as small incidental kidney tumours, certain *in situ* tumours or basal cell carcinomas. In contrast, depending on their type or stage, other tumours imply a certain waiting time free of disease. After analysing the different clinical situations, the Canadian Transplant Association recently published a series of guidelines which allow the recommendation of specific waiting timeframes that correspond to tumour type.

5. MAIN TUMOUR TYPES IN THE KIDNEY TRANSPLANT POPULATION

Posttransplant lymphoproliferative disorder (PTLD)

Posttransplant lymphoproliferative disorder (PTLD) is a well-recognized complication of both solid organ transplantation and allogeneic hematopoietic stem cell transplantation. It is one of the most common posttransplant malignancies. In most cases, PTLD is associated with Epstein-Barr virus (EBV) infection of B cells, either as a consequence of reactivation of the virus posttransplantation or from primary EBV infection. In cases of primary infection, EBV may be acquired from the donor graft or, less commonly, from environmental exposure.

According to different data, the incidence varies between 1% and 20% depending on immunosuppression regimen, type of organ transplanted and the presence of EBV infection.

Posttransplant lymphoproliferative disorders have a different histology, are more aggressive and generally have a worse prognosis. Most cases of PTLD occur within the first year after transplant, most seem to be related to EBV infection and mainly affect the transplanted organ.

The more intense the immunosuppression used, the greater the risk of PTLD and the earlier it tends to occur.

Cases that present with late onset are generally EBV-negative

Global mortality is generally high, ranging between 30% and 60% according to different authors. Factors associated with a better prognosis are a younger age at time of onset, a disease limited to a single site or to the graft, resectable lesions or lesions treatable by a reduction in immunosuppression. The worst prognosis involves forms that affect the central nervous system (CNS).

Diagnosis

PTLD is identified by a high index of suspicion in the appropriate clinical setting.

Early diagnosis is mandatory because of the high mortality rates involved and the non-specific forms at presentation.

This disorder can present in an impressive variety of guises. It can mimic relatively benign conditions in its presentation (such as mononucleosis or tonsillar hyperplasia), so a high degree of clinical vigilance and an awareness of its highly variable presentation are required to ensure diagnosis is not undetected.

Presentation of PTLD may be as single or multiple lesions which may affect both solid organs and lymph nodes.

For Bakker, given the frequency of extranodal presentation, one should consider clinical symptoms involving other organs including the graft itself. With kidney failure, hydronephrosis due to ureteral blockage and fever an ultrasound can easily detect the presence of enlarged lymph nodes or a badly defined kidney mass. Likewise, the onset of gastrointestinal signs and symptoms like diarrhoea or melena should raise the suspicion of bowel involvement.

Other non-specific signs may be encountered. These include fever of unknown origin or enlarged lymph nodes, headaches or confusion (due to CNS involvement), nasal blockage (sinus involvement) or ocular symptoms (affected sockets).

Eventually, PDLT may present with intestinal perforation or disseminated disease in otherwise asymptomatic patients. Non-specificity plus a variety of signs and symptoms are frequently confused with infections or adverse reactions to treatment. We may even encounter a total lack of symptoms, which makes diagnosis very difficult.

The most common diagnostic methods are:

» Imaging techniques: ultrasound, CT scan, endoscopy, magnetic resonance, and PET-CT, a more recent method, which is particularly useful in the detection of extranodal locations and evaluation of response to treatment.

» Histopathological evidence of lymphoproliferation, commonly with the presence of EBV, DNA, RNA, or protein detected in tissue. Determination of the EBV viral charge may have a positive predictive value, although a negative value does not rule out the risk.

Given the number of variables which influence the individual response of transplant patients, it is impossible to define a cut-off point that determines a critical EBV charge for PTLD development. Therefore, it is more appropriate to assess the detected increase in values so as to identify the individual risk per patient.

Treatment

The cornerstone of the initial management of PTLD is to reduce or withdraw immunosuppression. This may reverse the lymphoproliferative process in some situations, and it distinguishes PTLD from the neoplastic lymphoproliferative disorders that occur in immunocompetent patients.

Tapering immunosuppression also carries the risk of inducing allograft dysfunction or loss, and is not always feasible, depending on the grafted organ or clinical context.

Given the close relationship between PTLD and immunosuppression, restoration of the patient's immune competence seems critical. Therefore, a first treatment option should consist of reducing immunosuppression. Complete remission has been achieved using this strategy by itself or in combination with surgery or radiotherapy. However, immunosuppression reduction alone can induce a remission rate of only 25%.

Other PTLD treatment options include surgical resection when the lesion is localized, transplantectomy, local radiation therapy, antiviral therapy, immunoglobulin therapy, chemotherapy, interferon, monoclonal antibodies, and the use of cytotoxic T lymphocytes.

The choice of PTLD treatment will depend on its histology, location and biological activity.

» General practice is to use standard chemotherapy treatments (cyclophosphamide, doxorubicin, vincristine and prednisone-CHOP).

» Antiviral therapy has been tested, although it seems generally more effective as a prevention rather than treatment. Its use would be recommended for EBV-negative patients, especially if they had received a transplant from an EBV-positive donor.

» Rituximab (a humanized anti-CD20 monoclonal antibody) has shown benefits in the treatment of CD20-expressing non-Hodgkin lymphomas and PTLD. Although experience in transplant patients is, to date, limited, it shows benefits when used alone or combined with chemotherapy. A recent publication recommends its use for patients where a reduction in immunosuppression is not sufficient, particularly in EBV-positive patients. Due to its greater toxicity, chemotherapy should be reserved for patients who do not respond to rituximab and are EBV-negative or require rapid response.

Based on their potential anti-neoplastic activity, proliferation signal inhibitors (sirolimus/everolimus), have been tested, associating chemotherapy, anti-CD20 (rituximab) drugs or intensification with an autologous transplant from haematopoietic progenitors, which would enable graft maintenance.

Prophylaxis

In 2012, an international multidisciplinary panel of experts published a consensus statement on the classification and risk factors for PTLD, and outlined approaches to minimize the risk of developing PTLD.

The first of these recommendations from the Seville Workshop group is that the EBV status of both the donor and the recipient should be ascertained prior to donor selection. Whenever possible, EBV-negative recipients should receive grafts from EBV-negative donors.

The next suggestion is to minimize upfront immunosuppression as much as possible and potentially to use reactivation of other viruses, such as the CMV or BK viruses, as cues to reduce immunosuppression. Although antiviral therapy has not proven to be an effective treatment for PTLD, in selected high-risk patients prophylactic or preemptive antiviral therapy may be considered. An alternative approach to antiviral prophylaxis is to administer IVIG or Cytogam® to maintain high titres of anti-EBV antibodies that may help prevent the development of EBV PTLD.

The last recommendation from the Seville Workshop is to consider preemptive treatment for patients who appear to be developing PTLD. A rising EBV viral load in a high-risk patient may warrant a preemptive reduction in immunosuppression, while close monitoring for allograft dysfunction continues.

Immunosuppression

As previously seen, the type, duration and intensity of immunosuppressor treatment play a crucial role in the development of PTLD.

Use of CsA has been related with an increased risk of PTLD, attributable to immunosuppression aggressiveness. Conversely, proliferation signal inhibitors have shown an antitumoral protection role, without diminishing their immunosuppressor effect.

In experimental *in vivo* models, sirolimus has shown antiangiogenic activity linked to a reduction of the vascular endothelial growth factor and inhibition of vascular endothelial response to stimulation by the same factor.

Vaysberg et al. studied the mechanism whereby rapamycin inhibits proliferation of EBV infected B cells coming from patients with PTLD *in vitro* and *in vivo*, thus demonstrating the potential therapeutic effect of these drugs in PTLD, as well as in other EBV-positive lymphomas.

This antitumoral action was highlighted in a clinical study by Kaham et al., who found a much lower incidence of tumours in patients treated with sirolimus among a cohort of 1,008 kidney transplant patients. Moreover, Ghobrial et al. confirmed a high response rate in patients treated with rapamycin (58-62%).

Pascual published the clinical experience of nine European centres where a 78% remission rate (15 out of 19 PLTD patients) was obtained after converting immunosuppression to proliferation signal inhibitors after minimizing or eliminating calcineurin inhibitors.

Other authors have found a lower risk of PTLD when using MMF,31 that is thought to have an anti-tumoral activity due to its ability to reduce the binding of tumoral cells to the endothelium.

6. KAPOSI SARCOMA

The onset of Kaposi sarcoma generally occurs during the first-year posttransplant, is more common among the male population and is related to human herpesvirus 8 (VHH-8) infection. It may manifest as skin, mucosa and visceral lesions (including lymph nodes, gastrointestinal tract and lung).

Diagnosis

Symptoms include the appearance of red, purple or brown spots on the skin and/or mucosa, abdominal or intestinal pain, persistent cough or breathing difficulties and inflammation of lymph nodes or vessels.

In order to confirm the diagnosis, it is necessary to consult the medical history, undertake a physical examination, and consider performing biopsies on the mucosal and skin lesions. Imaging studies including X-rays, CT, MRI and any other imaging technique able to detect sarcomatous invasion should be conducted.

Given the high mortality rate, the periodical assessment of patients is essential for early detection of any suspect lesion. An annual check-up of skin and mucosa is recommended, although in higher-risk patients (due to ethnicity, geographical area or positive serology for HHV-8), more frequent revisions may be appropriate.

Therapeutic management

In common with PTLD, a reduction of immunosuppression plays a crucial role in the management of Kaposi sarcoma. Nevertheless, this must be balanced against the associated risk of graft rejection and secondary kidney failure due to underimmunosuppression.

The treatment of Kaposi sarcoma in the transplant patient is non-specific. A local approach is generally recommended and consists of surgical resection, radiotherapy, and intra-lesion chemotherapy. A systemic treatment with specific chemotherapy may also be required.

Moreover, recent studies that have shown the direct anti-tumoral effect of mTOR inhibitors encourage their use as part of immunosuppressive regimens. Different studies show the benefit of using proliferation signal inhibitors in patients with Kaposi sarcoma.

Immunosuppression

There is evidence to relate immunosuppressor treatment and HHV-8 infection with Kaposi sarcoma, although not all immunosuppressant treatments have the same effect.

It seems that CsA and nucleotide synthesis inhibitors, mycophenolate mofetil (MMF), favour its development, whereas proliferation signal inhibitors (everolimus, sirolimus) prevent it. This concept would be supported by works such as that of Stallone et al., which found that patients who had developed Kaposi during treatment with CsA, MMF and prednisone, reversed when the previous treatment changed to sirolimus.

7. SKIN CANCER

Skin is the most susceptible organ to tumour development in the transplant patient. Its incidence varies depending largely on the degree of exposure to sun.

Compared to the general population, onset is much earlier, and it usually presents with multiple tumours. Moreover, unlike the general population, these cancers have a greater tendency to recur (12% after ablation) and are much more aggressive (8% metastasis). Non-melanocytic tumours are the most common group, particularly basal cell epithelioma and squamous cell carcinoma. Basal cell carcinomas occur 65 to 250 times more frequently than among the general population, and squamous cell carcinoma about 10 times more.

Diagnosis

Diagnosis is based on characteristic skin lesions: flat or raised, ivory, red or pink, predominantly on sun-exposed areas for the basal cell carcinoma and fleshy red or pink lesions often with whitish scales on the skin for squamous cell carcinoma. When facing a suspicious lesion, a biopsy should be performed.

Therapeutic management

Skin cancer management should include prevention, care of premalignant lesions and treatment of already existing cancer.

In terms of prevention, the factors to consider are clearly related to the onset of cancerous lesions, such as exposure to sun, and additional factors that play a less important role, such as diet.

Thus, recommendations should include avoiding or limiting sun exposure, taking special care with the most exposed areas (head, neck, hands). As to diet, although there is less evidence, the recommendation is to increase vegetable intake and reduce consumption of fats.

In addition, prevention may include reducing immunosuppression for particularly susceptible patients while maintaining particular vigilance to the risk of acute rejection.

Along with periodical check-ups by a dermatologist, it is also important to teach the patient how to perform periodical self-examinations.

Bearing in mind that most squamous cell carcinoma epitheliomas develop from premalignant lesions (*in situ* carcinoma, actinic keratosis), it is important that all transplant patients should have preemptive specialized assessment.

Given the frequency with which these lesions may recur and/or become malignant, they should receive early treatment. Use of physical means like cryotherapy, photodynamic therapy or electrocoagulation is generally recommended. Topical or oral retinoids may be used on large lesions or to prevent local recurrences. More recently, immune response modifying drugs like imiquimod or resiquimod have been used.

Curettage, radiotherapy, cryosurgery, laser or photodynamic therapy may be used to treat superficial or initial skin cancer lesions. The use of topical immunomodulatory drugs, such as like imiquimod or resiquimod, have been tested on superficial basal cell epitheliomas with good results, and are also indicated.

For more advanced carcinomas, surgery remains the treatment of choice, and includes tumour excision and the reconstruction of affected skin. Histology will confirm diagnosis and indicate staging. When lesions are large, recurrent or affect facial skin, the recommendation is Mohs surgery, consisting of layer-by-layer lesion resection associated with intraoperative frozen sections. Resection continues until histology shows the absence of malignant cells.

When there is lymphatic involvement, a lymphadenectomy might be sufficient, or adjuvant radiotherapy might be necessary (if several lymph nodes are affected and there is extracapsular dissemination). Invasive cancers will require chemotherapy treatment following standard guidelines (bleomycin, fluorouracil and cisplatin). Reduction of immunosuppression is recommended in recurring squamous cell carcinoma epitheliomas, especially in those with metastasis.

Switching to everolimus/sirolimus would have a beneficial anti-tumoral effect while maintaining an appropriate immunosuppression state.

Immunosuppression

The relation between immunosuppression and skin tumours has been known since Walter et al. notified an increase in the incidence of skin tumours in kidney transplant patients in 1971.

Generally speaking, the incidence of skin cancer increases with the duration of the immunosuppressant treatment, suggesting a dosage-response relationship.

The use of CsA has been related to a higher risk of skin tumour, which is dose-dependent; azathioprine appears to reduce DNA repair, particularly in cells exposed to UV radiation.

Although the anti-tumoral properties of MMF have been proven *in vitro*, they have yet to be validated in animal or human models.

Other drugs such as proliferation signal inhibitors (mTOR) seem to be related to a lower incidence and also a better evolution of skin cancers. Although there is still little evidence, different studies have proved that replacing cyclosporine with everolimus or sirolimus is accompanied by the remission of skin lesions in a high percentage of patients.

8. SOLID ORGAN CANCER

As previously mentioned, transplant patients have a higher risk of developing cancer. According to Kasiske et al. [1], kidney cancer might occur up to 15 times more frequently than in the general population. Hepatobiliary, cervical or vulvo-vaginal tumours may increase up to five times and testicle and bladder tumours, three times more. Colon, lung, prostate, stomach, pancreas, ovary and breast tumours are approximately twice as frequent.

Bearing in mind the wide variety of tumours which could affect transplant patients it is important to consider prevention, as well as early diagnosis and treatment.

The European Code Against Cancer establishes recommendations for the prevention and early diagnosis of the disease, as well as cancer treatment in its earliest stages.

CONCLUSIONS

The occurrence of tumours in transplant patients is even more frequent due to factors like age, greater life expectancy and the use of efficient immunosuppressant treatments.

The relative risk of suffering from a tumour is higher than for the general population, from twice as often for the most common tumours in the general population (colon, lung, prostate, etc.). It can reach a risk of up to five times higher for melanoma, hepatobiliary, cervical and vulvo-vaginal tumours, or may even be twenty times higher for non-melanocytic skin cancer, Kaposi sarcoma and non-Hodgkin's lymphoma. The global mortality due to cancer is 9-12%, and the average survival for patients with cancer is 2.2 years.

All of which show the importance of the prevention, early diagnosis and correct treatment of this disease. In order to prevent we need to recognize the risk factors associated with different tumours and minimize them as much as possible.

Immunosuppressive therapy plays an important role, and we have seen that while certain immunosuppressants may favour the development of cancers, others might prevent or reverse them.

Dialysis and transplant patients should receive early diagnosis by means of periodical clinical evaluations to detect any tumour in its earliest stages. As for treatment, the application of specific guidelines for each tumour type and the correct management of immunosuppressant therapy both play an important role.

The antiproliferative features of mTOR make them potential anti-neoplastic drugs for transplant patients and their role in the inhibition of oncovirus replication like EBV has been proven. *In vitro* and *in vivo* studies have proven this anti-neoplastic effect, which is being clinically corroborated in an ever-greater numbers of publications that demonstrate the benefits of using mTOR in cancer patients. These studies show a lower tumour incidence as well as a high remission rate when switching to sirolimus/everolimus. This will ultimately imply suppressing and/or minimizing CNIs (tacrolimus and CsA) to enable the implementation of specific anti-tumoral therapy. Several studies show the efficacy of this approach in the prevention of graft failure as well as its overall good tolerance.

Although it is premature to make recommendations based on what is still a limited body of data, we can state that the everolimus/sirolimus drug group appears to offer a promising therapy in the prevention and treatment of the transplant patient's malignant lesions.

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TOPIC 1 - Unit 3

Anaesthesiology in transplantation

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INTRODUCTION

Depending on the type of organ transplantation, every transplant patient undergoes a specific type of anaesthesiology and immediate postoperative follow-up.

This unit focuses on the different points that require attention depending on the organ to be transplanted. In addition, it discusses details of waiting list management and urgency listing for certain organs. This matter is important when deciding the best possible approach in terms of the patient's urgency status.

1. LIVER

To date liver transplantation is the most successful treatment of, and only definitive treatment for, patients for whom medical treatment has failed [1].

When the first transplant programmes began at the end of the 1960s, surgical and anaesthetic complexity was a huge challenge, the most important aspect of which was achieving the patient's immediate survival. New immunosuppressor drugs, developments in surgical techniques and changes in intraoperative anaesthetic management, mean that despite being one of the largest and most complex surgeries, liver transplantation now constitutes a routine surgery performed in many centres, with pursual of quality objectives once intraoperative survival outcomes have been achieved.

This chapter deals with intraoperative anaesthetics and the reanimation management necessary to perform this surgery.

1.1 The physiopathology of hepatic disease

Hepatic disease causes a series of changes in multiple organs and systems. From an anaesthetic perspective, it is important to the understand changes that occur in the cardiovascular (haemodynamic), renal and respiratory systems, as well as changes in coagulation, glucose metabolism, serum acid-base balance and electrolyte balance.

The cardiovascular system

Micro-alterations and fibrosis in the liver cause hepatic blood flow obstruction with an increase in portal pressure. Portal hypertension is accompanied by an increase in vasodilatation substance circulation levels, metabolism deficit and the need for portosystemic shunts.

This causes splanchnic arterial vasodilation that induces a hyperdynamic state with drop in central blood volume. This activates the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), with an increase in levels of copeptin, a vasopressin precursor. This hyperdynamic cardiovascular state is characterized by an increase in heart rate, cardiac output and plasmatic volume accompanied by a drop in systemic vascular resistances and blood pressure. Figure 1 summarizes the physiopathological changes that trigger this hyperdynamic state.

All these changes play an important physiopathological role in the development of complications of cirrhosis. Portal hypertension, together with alterations of permeability and intestinal capillary pressure, like RAAS and SNS activation, are involved in the onset of ascites and the deterioration of kidney function, with a reduction in water and sodium excretion. Decreased albumin production also contributes to ascites. If kidney deterioration progresses, patients will present diluted hyponatraemia, and finally hepato-renal syndrome (HRS). The appearance of oesophageal varices through which blood from the splanchnic region passes to systemic circulation is secondary to the presence of portal hypertension, and frequently the cause of digestive haemorrhage in these patients. Moreover, the deterioration of hepatic function together with portosystemic shunts may cause an increase in toxin and ammonium levels, which may trigger hepatic encephalopathy [2].

In recent years, cirrhotic cardiomyopathy has been described as a specific condition that affects approximately 50% of cirrhotic patients. It is characterized by an apparently normal heart at rest but with a bad response under stress. Diagnostic criteria were proposed in 2005, however, they have not undergone the scientific validation necessary to establish a diagnosis [3].

» Systolic dysfunction: Impaired cardiac output (CO) with exercise, volume overload or pharmacological stimulus. Left ventricle stroke fraction at rest <55%.

» Diastolic dysfunction (ultrasound diagnosis): Prolonged deceleration time (>200 ms), prolonged isovolumic relaxation time (<80 ms), E/A ratio <1 (E being premature ventricular filling and a ventricular filling secondary to atrial contraction).

» Additional criteria: Electrophysiological anomalies, abnormal chronotropic response, prolonged QT interval, dilated left atrium, myocardial mass increase, and an increase in levels of BNP, proBNP and troponin I.

The onset of cardiomyopathy is independent of the aetiology of cirrhosis, although the former is related to its severity of the latter. Cardiomyopathy is usually subclinical but becomes patent in stress situations, for instance, any intervention such as the insertion of a transjugular intrahepatic portosystemic shunt (TIPS) or a liver transplant. The insertion of a TIPS causes a brusque increase of preload that may cause a diastolic dysfunction that triggers cardiac insufficiency. The systolic dysfunction observed in advanced stages with low cardiac output is related to the onset of HRS. Treatment is non-specific and necessary support measures should be taken [4]. It should be highlighted that this condition is reversible and once transplanted, these cardiac changes may revert in less than one year [5].

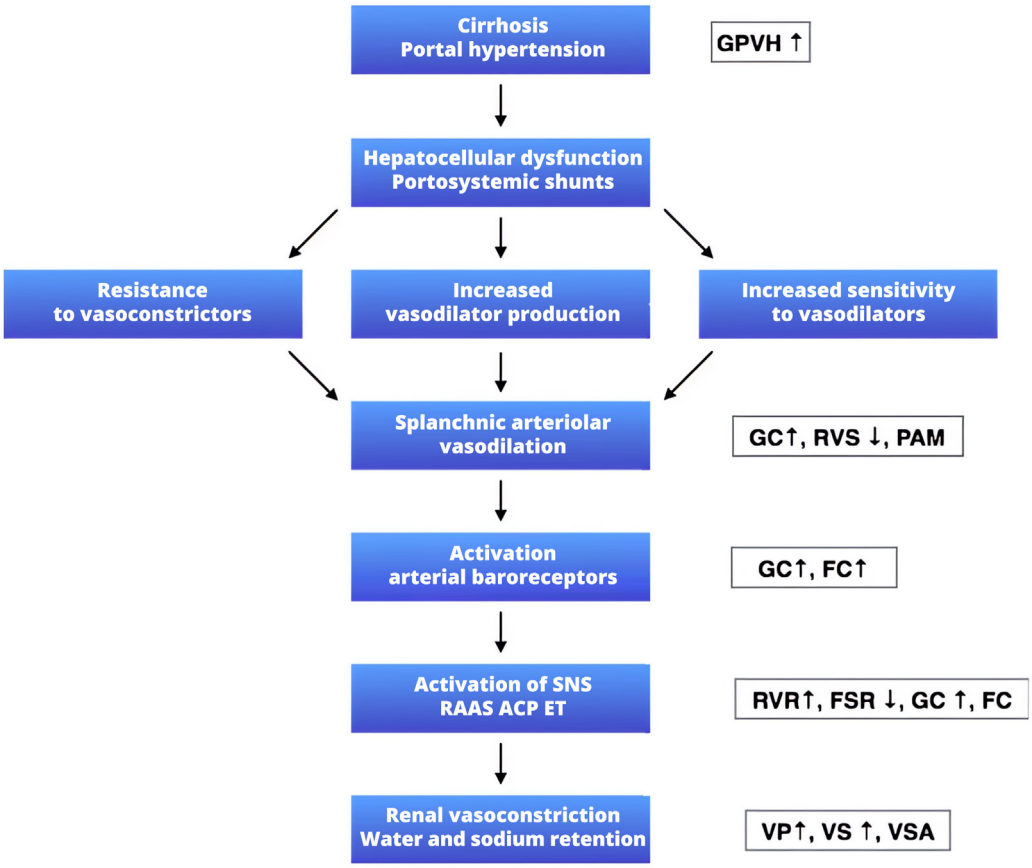

Figure 1. Physiopathological changes triggering the hyperdynamic state. HVPG = hepatic venous pressure gradient, CO = cardiac output, SVR = systemic vascular resistance, MAP= mean arterial pressure, HR = heart rate, SNS = sympathetic nervous system, RAAS = renin-angiotensin-aldosterone, AVP = vasopressin, ET = endothelin, RV = renal vascular resistance, RBF = renal blood flow, PB = plasmatic volume, BV = blood volume, ABV = arterial blood volume.

Respiratory system

Patients with cirrhosis who develop ascites, frequently present restrictive pulmonary symptoms which may worsen with the presence of hydrothorax. Hydrothorax occurs in 5-12% of patients with hepatic disease, tending to occur on the right side, but unrelated to pulmonary or heart disease. An accumulation of transudate usually occurs at pleural level due to a diaphragmatic defect and always in the presence of ascites.

Chronic obstructive pulmonary disease (COPD) is not a complication of cirrhosis, although it is common in these patients, given its association with drinking, one of the primary causes of hepatopathy in our society, and smoking. Approximately 18% of liver transplant candidates have COPD.

The literature describes two pulmonary vascular abnormalities typical of patients with hepatic disease that are different and apparently opposing, although exceptionally they may co-exist. Physiopathologically they are triggered due to an imbalance between vasodilator and vasoconstrictor substances, with the onset of hepatopulmonary syndrome (HPS) if vasodilators predominate, and portopulmonary hypertension (PPHT) if vasoconstrictors predominate.

The chronic hepatic disease combination, i.e., gaseous interchange alteration (oxygen alveolar-arterial gradient >15 mmHg) and intrapulmonary vasodilation [6] defines HPS and is prevalent in 20% of liver transplant candidates. It has no specific signs or symptoms, however the presence of hepatic disease with signs of hypoxemia (cyanosis, nail-clubbing, SaO_2 <96%) should alert us to suspect its presence. Liver transplantation is the only effective treatment for HPS.

The definition of PPHT is the presence of pulmonary arterial hypertension in a patient with portal hypertension where no other possible cause of pulmonary hypertension exists. Diagnosis is made via right cardiac catheterization with findings of a mean pulmonary arterial pressure MPAP >25 mmHg at rest with pulmonary vascular resistance >240 dyn.s.cm [6]. The incidence of PPHT is 4%, and it is associated with high morbidity and mortality in liver transplantation pre-operation when it is moderate (MPAP >35) or severe (MPAPM >50) [7].

Haemostatic system

Patients with hepatic disease present important haemostatic abnormalities and are classically considered disposed to haemorrhage. However, recent papers suggest that rather than a coagulation defect, in the cirrhotic patient there is a haemostatic rebalance due to a deficit and/or alteration of pro-clotting and clotting inhibitor substances. Under certain circumstances, such as infection or kidney failure, this new imbalance may alter blood flow or provoke endothelial activation, which puts the patient in a prothrombotic situation, predisposed to haemorrhage [8].

The literature describes numerous alterations that affect haemostasis in cirrhotic patients. Worthy of note among the factors that predispose to haemorrhage are thrombocytopenia and platelet function defects, an increase in nitrous oxide production and prostacyclin, a drop in coagulation factors II, V, VII, IX, X and XI, vitamin K deficit, dysfibrinogenemia, low levels of alpha-2-antiplasmin, factor XIII and TAFI, and elevated tPA levels.

Among the factors that may trigger thrombosis note should be taken of high levels of VWF, a drop in ADAMTS-13 levels, an increase in factor VIII, a drop in C protein, S protein, antithrombin, 2-macroglobulin and heparin cofactor II, and low levels of plasminogen [9].

Glucose metabolism

Terminal cirrhotic patients present insulin resistance with an increase in both insulin secretion and in glucagon levels.

Glucagon has important cardiovascular effects, such as increasing heart contractility and frequency, with a subsequent cardiac output, in addition to splanchnic vasodilation that is refractory to vasoconstriction mediated by noradrenaline, angiotensin or vasopressin.

Basal glucose levels are high in comparison to those of the general population, and response to glucose overload is exaggerated, with a presence of hyperglycaemia and hyperinsulinemia. Resistance to insulin in the cirrhotic patient is due to alteration of glucose availability for the musculoskeletal system, due to muscle difficulty in synthesizing glycogen and oxidating glucose.

In both healthy and cirrhotic people 60% of the glycolytic pathway turns into CO_2 and 25% into lactate.

Lactate flow at rest is approximately 2-3 µmol/kg/min with 40-50% of lactate capture, which equals its basal production, occurring in the liver, 30% in the kidney and 20% musculoskeletal. Both kidney and muscle have a limited lactate elimination capacity, which worsens with hepatic disease. Lactate captured by the liver is incorporated in glucose (70%) or oxidized to CO_2 (30%). This cycle between glucose and lactate, called the Cori Cycle, enables constant glucose levels to be maintained in the organism during fasting and ingestion.

The cirrhotic patient is able to maintain normal lactate flow. However, due to a reduction in hepatic clearance of lactate, these patients do not respond correctly to increases in lactate. Moreover, they present an abnormal response to glucose overload and produce more lactate per gramme of glucose. For this reason, and due to the risk of infection, these patients are more susceptible to the onset of lactic acidosis.

Alterations in acid-base and serum electrolyte balance

Most patients with hepatic dysfunction have a neutral acid-base balance. Some patients may present respiratory alkalosis mediated via the CNS. Patients under treatment with furosemide or thiazides may present metabolic alkalosis accompanied by hyperkalaemia. They very rarely present metabolic acidosis secondary to liver failure to clear lactate or due to the kidney's incapacity to retain bicarbonates.

Cirrhotic patients usually present hyponatremia due to free water retention exceeding sodium retention. Bear in mind that too fast a correction of plasmatic sodium levels risks the onset of CPM with devastating consequences [10].

Serum potassium levels may be high, normal or low. Hypokalaemia may be secondary to the administration of diuretics (furosemide or thiazide). Hyperkalaemia may be secondary to metabolic acidosis in treatment with K+ -saving diuretics, where there is an interchange between intracellular K+ and extracellular H+ or kidney failure.

Calcium levels are usually normal. The administration of blood components rich in citrate may produce chelation of Ca++ with a drop in its plasmatic levels [11-13]. Mg++ levels are usually normal but may decrease if the patient presents deficient nutrition [14].

1.2 Preoperative evaluation of the liver transplant candidate

The number of patients suitable for liver transplantation has changed in recent decades thanks to demographic changes combined with positive results in liver transplantation. In the past, transplant patients were younger and without associated pathologies, whereas today's patients are older and have more comorbidities. This increase in transplant recipients means an insufficient supply of livers to cover all needs. Therefore, achieving both maximum patient survival and graft survival have become priorities.

The two basic aims of preoperative evaluation are: 1) An individual stratification of surgical risk, which is essential to exclude patients whose associated pathology involves a serious increase in surgical risk. 2) An estimation of the long-term prognosis, considering the patient's associated pathologies, to establish the risk-benefit ratio of the procedure [15]. In this sense, it is essential to estimate the patient's life expectancy, conditioned by the natural history of their disease, to determine the real benefit of transplantation. A patient's life expectancy should exceed 10 years for them to be a candidate for a liver transplant.

Preoperative evaluation should pay particular attention to the cardiovascular and respiratory systems.

Cardiological evaluation

Cardiological evaluation must aim to detect and stratify ischaemic heart disease and cirrhotic cardiomyopathy. Moreover, given the risk associated with the surgery itself, other pathologies that determine risks of mortality and morbidity must be excluded. These include, for instance, valvular disease, restrictive cardiomyopathy and the presence of arrhythmia in patients with genetic amyloidotic polyneuropathy.

Hepatic disease was traditionally considered a protective effect against coronary disease. However, recent papers show that the prevalence of coronary disease in this population is similar to that of patients undergoing other surgeries. Furthermore, posttransplantation immunosuppressive treatment will have an amplifying effect and predispose to hypertension, diabetes and dyslipidaemia.

Moreover, the basic cardiac workup, screening, and thorough clinical history to detect cardiovascular risk factors and estimate functional capacity should include an ECG and echocardiogram. Patients with coronary disease risk factors and/or low functional capacity should undergo a heart stress test (stress echocardiogram with dobutamine or myocardial perfusion scintigraphy with SPECT). If the stress test is positive, a coronary angiography is required to confirm the course of action.

To date, there is no test capable of diagnosing cirrhotic cardiomyopathy and most patients are diagnosed when cardiac insufficiency symptoms appear under conditions of stress. The diagnosis of diastolic dysfunction is possible with a Doppler analysis of mitral valve entry flow. If the E/A ratio (where E is premature filling and A is ventricular filling due to atrial contraction) is under 1, this may mean diastolic dysfunction. Diastolic dysfunction usually precedes systolic dysfunction, which may be diagnosed by means of LV stroke fraction. The atrial natriuretic factor B-type natriuretic peptide (BNP) and troponin I are frequently elevated in cirrhotic cardiomyopathy. Thus, diagnosis of cardiomyopathy will depend on the presence of systolic and/or diastolic dysfunction plus other criteria like electrophysiological abnormalities and the presence of serological markers.

Respiratory evaluation

The high prevalence of respiratory problems in the cirrhotic population in addition to the complexity of transplant surgery require an extensive respiratory evaluation which, as well as the clinical history and a physical examination, must include a simple thorax X-Ray and a complete pulmonary function evaluation with arterial gas analysis.

For COPD patients, functional respiratory tests will determine the severity of the disease by defining airflow obstruction (FEV_1). However, in moderate or severe cases, determination of the pulmonary disease's prognosis and the evaluation of its severity should be completed with other examinations. The BODE

index [16], which includes BMI, FEV_1, dyspnoea, and exercise capacity using the 6 minute walking test, has proven to be a highly efficient tool in determining death risk due to respiratory and non-respiratory causes in COPD patients.

Hydrothorax may cause dyspnoea or hypoxemia, which resolves after transplantation, so it is never an absolute contraindication. Its functional impact is well reflected in the results of pulmonary functionalism. Exceptionally, preoperative draining is required if respiration is compromised. In the preoperative evaluation it is important to rule out other causes of pleural effusion such as infection, thromboembolic disease or metastasis.

There should be a suspicion of PPHT in the presence of a prominent pulmonary vascular tree or right branch obstruction in a simple chest X-ray. An echocardiogram is considered a good method for excluding patients with PPHT. The mortality associated with a transplant in the presence of PPHT is close to 100% in the case of serious hypertension, so this pathology should be a contraindication. Should an echocardiogram estimate a right ventricle systolic pressure above 38 mmHg, a right-side catheterization is compulsory. Diagnosis is compulsory if mPAP is >25 mmHg with normal capillary pressure (<15 mmHg) and pulmonary vascular resistance is over 240 dynes/sec/cm^{-5}. Indeed, mPAP >45 mmHg is considered a contraindication for transplant. Nevertheless, if pulmonary arterial pressure reduces after several months of specific vasodilator therapy, the patient may be reconsidered for transplant. The use of specific therapies has considerably reduced the prognosis for these patients [17] so they should be treated prior to transplant. Evaluations of right ventricle function and cardiac output are other aspects to consider when making a decision [18].

Patients with HPS frequently also present cutaneous stigma of cirrhosis, i.e., nail clubbing, cyanosis and hypoxemia, which can be detected by the presence of oxygen arterial saturation (SaO_2) <96% breathing air [19]. Diagnosis should be made with an echocardiogram which shows the late pass of micro air bubbles injected via a peripheral vein to left side cavities, or with the extra pulmonary capture of macro aggregates of albumin marked with technetium 99 (^{99m}TcMAA) [20]. Patients with arterial values of PaO_2 <50 mmHg will require individual analysis as they have a higher post-operation morbidity and mortality [6]. PaO_2 <60 mmHg is considered a major criterion on the transplant list due to its bad prognosis if not transplanted. Severe hypoxemia (between 50 and 60 mmHg) is not only a major reason but also the primary indication for liver transplant as syndrome cure has been proven after transplant [21, 22].

1.3 Donor and recipient changes: the impact of implantation on MELD score and making use of suboptimal donor livers

Positive transplant outcomes in conjunction with an increase in the number of recipient candidates for organs quickly led to an imbalance between supply and demand. At the same time, Spain experienced a drop in the numbers of donors as a result of stricter road safety laws and the use of helmets becoming compulsory for motorcyclists.

On the one hand, this situation has led to the need for a greater supply of organs and broader organ acceptance criteria, particularly in terms of age limits and organs with slight abnormalities.

On the other hand, the creation of an index to classify patients means that livers are used for the most serious patients, rather than those who have spent the longest time on the waiting list. The Model for End-stage Liver Disease (MELD) system, uses three simple analytical, objective, reproducible parameters (bilirubin, creatinine and INR) in its calculation and correctly relates the mortality of patients with chronic hepatopathy of any aetiology [23], so its use has become generalized to decide the position of candidates on the liver transplant waiting list.

One of the biggest successes of MELD's application has been a reduction in the waiting list death rate, with transplant survival rates similar to previous ones [24-26]. However, the clear benefits of using MELD to optimize the waiting list in conjunction with obtaining livers from suboptimal donors mean that the patients who undergo liver transplant are sicker (have a more advanced hepatopathy with a higher per-

centage of kidney failure and coagulopathy). Moreover, recipients will probably receive an older organ, with less optimal function than the livers transplanted 20 years ago. This combination means we see more haemodynamic and coagulation abnormalities and more intraoperative post-perfusion syndrome, i.e., patients with a more complicated perioperative management.

1.4 Intraoperative management

Liver transplant stages

Almost half a century since the first liver transplant, the development of surgical techniques and advances in the field of anaesthesia have led to important changes in the intraoperative management of these patients.

The anaesthetic chronology of a liver transplant begins with anaesthetic induction, invasive monitoring and the insertion of large calibre venous ports. Next, surgery begins with three clearly differentiated stages:

- Hepatectomy, when the surgeon opens the abdominal cavity, dissects hepatic hilum and extracts the liver.
- Anhepatic stage, when the graft is inserted, anastomosis is performed on supra-hepatic veins with vena cava and portal anastomosis. During this phase, the liver is not connected to the patient's vascular system. This stage ends when the clamps are opened allowing blood to flow through the implanted liver.
- Neohepatic stage, from reperfusion, when anastomosis is performed on the hepatic artery and bile duct, haemostasis is reviewed, and the abdominal cavity closed.

During the anhepatic stage the liver is not vascularized and, depending on the surgical technique used, there may be large haemodynamic alterations. In the early years of liver transplantation, the liver was extracted together with the retrohepatic vena cava, making it necessary to clamp the suprahepatic cava and the lower cava territory above the kidney veins. The haemodynamic consequence of total clamping is a marked reduction of venous return from the entire lower vena cava territory, which is not total because blood can return to the heart through the multiple collateral vessels that develop in the cirrhotic patient. However, there is a general drop in preload, cardiac output and blood pressure. Moreover, there is venous blood stasis in the entire lower vena cava system with increases in venous pressure, the consequence of which are an increase in surgical haemorrhage that favours the onset of intestinal oedema, jeopardizing surgical intervention at that time. Likewise, an increase in venous pressure at lower vena cava causes a pressure increase in the kidney's venous system and a drop in renal perfusion with serious mortal effects on this organ's function.

The venovenous bypass (VVB) was introduced in the early 1980s, and greatly helped the intraoperative metabolic and haemodynamic management of these patients [27]. This bypass consists of inserting a venous cannula in the lower cava territory, usually the femoral vein, with another cannula in splanchnic territory, usually a mesenteric vein, serving to drain these territories. Via a cylinder pump, infra-diaphragmatic venous blood bypasses the vascular clamp of the cava towards another cannula, inserted in an arm or neck vein, towards the upper vena cava territory and the heart. This technique achieves greater haemodynamic stability by maintaining heart preload, minimizing oedema and haemorrhage, and avoiding impact on kidney function. However, it is not without side effects. On the one hand, it increases surgery time, and on the other, described complications include venous thrombosis, thromboembolism, and vascular lesions among others. The VVB was widely used in the USA, while in Europe many groups preferred vascular exclusion of the liver, using the bypass solely in selected cases or when the patient did not tolerate vascular exclusion.

At the end of the 1980s, the cava preservation or "piggyback" technique was described [28] which dissected the liver from the retrohepatic vena cava, enabling maintenance of the venous return flow at all times

from the lower vena cava to the heart. This technique brought a clear improvement in both haemodynamic and metabolic stability as well as a reduction in intraoperative haemorrhage.

The subsequently described temporary portocaval shunt technique was enables drainage of blood from the splanchnic territory to the cava during the anhepatic stage. This shunt is performed on clamping the portal vein and undone on inserting the new graft [29]. It improves the patient's haemodynamic situation, reduces transfusion requirements and preserves kidney function during liver transplant.

Special devices used during transplant

To improve surgical technique and facilitate exclusion of the risk of a major haemorrhage involves a series of special techniques and devices, whose use is not exclusive to transplantation, but without which we would not consider performing this procedure.

- **Venovenous bypass (VVB):** Although piggyback is currently used in most cases, venovenous bypass is still a possibility, and it is therefore essential to have this system and appropriately trained staff available.
- **Cell Saver®:** A blood recovery system. It collects blood from aspirators, subjects it to lavage and concentration. This process enables autotransfusion of the patient's blood. Its use is contraindicated in the event of abdominal infection or neoplasia (hepatocarcinoma).
- **Rapid infusion system (RIS):** A perfusion pump enabling administration of a large volume in a short time. The infusion speed is adaptable to a maximum of 500 ml/min. Liquids that have previously been mixed in a reservoir (usually blood, plasma, serum albumin and crystalloids) are heated to 36ºC and administered via large calibre cannula 8-8.5F.
- **Point of care:** Laboratory parameter determination device located in the operating theatre that enables analysis with almost immediate results. It avoids having to send samples to the laboratory, which always involves a long delay. Typical analyses include arterial blood gas, complete blood count, clotting and basic biochemistry.
- **Thromboelastography (TEG) and thromboelastometry (TEM)** [30]. These are two similar techniques used to measure blood clotting efficiency which employ a vertical pin in a blood-filled cuvette. In TEG, the cuvette alternatively oscillates clockwise and anticlockwise while a clot forms between the pin and the

interior cuvette walls, resulting in a par torque in the pin converted into an electrical signal. In ROTEM, oscillatory force is transmitted to the pin while the cuvette remains stationary. As the clot is formed, pin oscillation reduces and is measured via the deviation angle of a light ray aimed at the pin. While classic laboratory tests serve to measure the function of different clotting factors, these systems provide us with information about platelet function, clotting force, and the possible onset of fibrinolysis, which is undetectable by other means. The possibility of having this type of a device in the operating theatre enables the availability of highly reliable results in 20-30 minutes.

Intraoperative monitoring

Invasive monitoring is essential during liver transplant. Haemodynamic, haematological and metabolic alterations are very common and oblige us to perform invasive monitoring of multiple values for early detection of abnormalities, and also guide the perioperative treatment of these patients.

Haemodynamic monitoring [31]: Besides the standard monitoring of any anaesthesia, invasive arterial pressure requires monitoring, usually using the radial artery. Furthermore, a second arterial line is advisable, if possible, in the femoral artery. This enables ongoing monitoring even *in situ*ations with major haemodynamic changes, when a line may be needed to draw blood samples.

Moreover, during the course of long surgeries, it is not unusual to face problems with regard to the re-

liability of measurements, due to flow changes and changed curves. Finally, *in situ*ations of extreme instability like vasodilation, which occurs after graft reperfusion, radial artery pressure readings give lower values than aortic pressure. It is generally considered that aortic pressure provides a more reliable value on the perfusion pressure of vital organs.

Although central venous pressure (CVP) is currently considered somewhat unreliable for the determination of intravascular volume, during transplantation it provides information on the status of the vena cava. It is also important to maintain low CVP values in order to minimize surgical haemorrhage. Although not common practice in many centres, monitoring of femoral venous pressure (FVP) provides valuable information to interpret haemodynamic changes secondary to preload variations caused by vena cava compression at liver level (increases in the gradient between upper and lower cava) or hypovolemia (normal gradient maintained). Likewise, when the surgeon places the temporary clamp to perform anastomosis of the suprahepatic veins with the cava, it is possible to see whether sufficient calibre is left to maintain acceptable venous return flow to the right atrium.

Although some controversy exists regarding use of pulmonary artery catheters (PAC) in liver transplants, a large number of medical teams continue using it. Less invasive systems currently exist to determine cardiac output and monitors of volume are more accurate than filling pressures to determine preload status. Furthermore, some studies describe a higher incidence of ventricular arrhythmias during PAC insertion in cirrhotic patients undergoing liver transplant. However, PAC monitoring enables diagnosis and management of PPHT, a pathology that is infrequent but with a high intraoperative mortality. The monitoring possibility of oxygen mix venous saturation SvO_2 via PAC provides additional advantages related to changes in cardiac output, O_2 transportation (Hb), as well as its contribution and demand. If PAC is not used, another cardiac output measuring system is required that uses analysis of the pulse wave contour, such as LiDCOplus® (Lidco UK), PiCCO® (Pulsion Germany) or VolumeView® (Edwards US). These systems enable monitoring of the patient's cardiac output and intravascular volume status. The cardiac output measurement of these systems is comparable to that of PAC, even for hyperdynamic patient.

Another, less invasive form of evaluating cardiovascular status is use of transoesophageal echocardiogram TEE. The initial reticence to employ this method was due to the risk of causing a digestive haemorrhage in cirrhotic patients with oesophageal varices, however, this is an uncommon complication. Use of TEE enables fast analysis of the function and size of the 4 chambers. The area index at the end of the left ventricle diastole in the trans-gastric view correlates well with acute hypovolemia, although the transgastric plane cannot always be viewed during liver transplant. Finally, in the case of embolism, particularly during reperfusion, TEE allows us to view the situation. Today it is considered the best cardiovascular monitoring technique during liver transplant [31].

Non-haemodynamic monitoring

As with any surgery, temperature monitoring is essential both for prevention and treatment of hypothermia.

Biochemical monitoring should include glucose, Na+, K+, Ca++, Mg++, lactate and creatinine. Haemoglobin and platelets should also be monitored. Serial analytical controls are advisable at the start of the intervention, on termination of hepatectomy, after liver reperfusion and at the end of surgery.

Other aspects that require monitoring are clotting, prothrombin time determination, cephalin and fibrinogen time with TEG or ROTEM, which should be available. As is the case with biochemistry, at least one analysis should be conducted at the start of the procedure, on termination of hepatectomy, after liver reperfusion and at the end of surgery.

Anaesthesia

The question of whether anaesthetic drugs have a hepatic metabolism does not have great importance in this surgery. On the one hand, patients will receive a new liver capable of metabolizing them, and on the other, in most centres, patients are still sedated when taken to ICU, where they are intubated and ventilated, so there will be sufficient time to metabolize anaesthetic drugs before extubation.

The choice of anaesthetic drug is essentially conditioned by patient's haemodynamic situation. Drugs with vasodilator and/or myocardial depressors should be avoided, and the dose should be carefully calculated.

Anaesthesia is usually maintained with a halogenated agent guided by bispectral index (BIS), and intraoperative analgesia with fentanyl.

Haemodynamic and metabolic changes during liver transplant

- **Hepatectomy stage:** Hepatic loss can be observed that is directly related to the degree of portal hypertension, the existence of prior surgery with adherences and neo-vascularization that will severely complicate dissection. If piggyback and temporary portocaval shunt are performed, large haemodynamic alterations are not expected during this stage. During portal vein clamping there is usually a decrease in cardiac output due to a drop in preload from the splanchnic territory. If necessary, administer vasoactive drugs like noradrenaline (NA), and volume replacement should follow a restrictive regime. Oligo anuria requiring diuretics is relatively frequent among these patients. It is also common for them to present onset of hyponatraemia, which is only partially corrected in the event of very low values (Na <130 mEq/L).
- **Anhepatic stage:** During this stage, the liver is not connected to the vascular system, consequently there is lactate accumulation and a tendency to metabolic acidosis. It was traditionally thought that hypoglycaemia might exist in this stage, however, this is very rare, and no extra contribution of glucose is required except in patients with acute liver failure. It is necessary to maintain K+ at the lower end of normal range to prevent a very sharp increase with reperfusion of the new graft.
- **Reperfusion syndrome (RPS):** This appears during graft reperfusion, is characterized by a drop in mean arterial pressure in excess of 30%, appears in the first 5 minutes after reperfusion and lasts over a few minutes. Its incidence is approximately 25%. The release of clamps on the portal and cava are responsible for an initial increase in filling pressures. If there is no cardiopathy, it responds by increasing cardiac output. Subsequently, there is a release of substances accumulated in the graft during the ischaemic period, with residual liquid preservation (cold and rich in potassium) into the circulation, which are responsible for the onset of bradycardia, arrhythmia and a drop in systemic vascular resistances resulting in systemic hypotension. To minimize this, some centres wash intrahepatic vessels with serum at room temperature prior to reperfusion, whereas others, depending on the perfusion solution used, perfuse with another solution on the back table to avoid hyperkalaemic states. Among prediction factors for the onset of this syndrome are an absence of temporary portocaval shunt, duration of cold ischaemia time and left ventricle diastolic dysfunction [35,36]. Suboptimal livers are also thought to increase the incidence of onset of RPS, augmenting kidney failure and post-operation mortality [35,36]. Treatment consists of an adrenaline bolus and NA perfusion until normal arterial pressure values are obtained. It is relatively frequent to reach this stage with metabolic acidosis, which is not usually corrected because once a graft is perfused and starts working it will metabolize the lactate causing metabolic alkalosis. During reperfusion a K+ peak is usual, which may reach values of 7 mEq/L but quickly normalizes after several cardiac cycles, Ca++ and Mg values should also be corrected if they are not within normal values.
- **Neohepatic stage:** During this stage, as the liver starts functioning, lactate accumulated during the anhepatic stage starts metabolising. Graft reperfusion releases glucose, resulting in hyperglycaemia that requires administration of endovenous insulin. The greatest clotting deterioration usually occurs during this stage. On the one hand there is a drop in platelet count due to hepatic endothelial

adhesion, and on the other, fibrinolysis may occur, which is detected via TEG, TEM and the presence of diffuse haemorrhage. Treatment is with tranexamic acid. Arterial pressure normalizes progressively, and NA perfusion can be reduced.

On completion of surgery patients are admitted to the ICU, where they will recover from anaesthesia and be extubated once no bleeding and haemodynamic stability have been confirmed.

Management of intraoperative transfusion and coagulopathy

Liver transplant surgery is always associated with a considerable blood loss and very high transfusion requirements. Despite this, over the years there has been a notable drop in haemorrhage and the number of blood derivatives used. When transplant programmes began, the mean number of red blood cell (RBC) concentrates transfused per transplant was 20, whereas today it is 2 or 3. Multiple factors have enabled this dramatic drop, among which are better knowledge of haemostatic changes in the cirrhotic patient, improved surgical technique and anaesthetic management of these patients.

Risk factors predictive of transfusion during liver transplant:

- Preoperative haemoglobin levels.
- Hepatic disease severity using Child-Pugh or MELD.
- Altered clotting tests during preoperative stage.
- Surgical technique (piggyback associated with less haemorrhaging) and prior abdominal cavity surgery.
- Elevated cold ischaemia time and suboptimal donors.
- Number of transplants per year performed at the centre.
- Surgical and anaesthetic experience of the medical team.

Currently the latter two factors are considered more important and are closely related to the variability of transfusion practices, not only between centres but also between doctors at the same hospital. For example, there may be different transfusion triggers or differences in clotting disorder management and its treatment with PPF, platelets, etc. Finally, not administering anti-fibrinolytics, whose usefulness has been demonstrated in liver transplant, may also be a factor which increases perioperative haemorrhage.

In recent years, since the publications of Reyle-Hant [37] and Massicotte [38], maintaining a low CVP, particularly during hepatectomy, is generalized, as is a restrictive liquid regime and avoiding the prophylactic correction of clotting abnormalities. The purpose of this strategy is firstly to reduce pressure in the splanchnic territory so as to avoid haemorrhage, and secondly, to avoid the dilution of coagulation and platelet factors. Part of the severe haemorrhage these patients suffered during transplantation was due to an increase in vascular volume secondary to the administration of liquids and blood derivatives. This created a vicious circle, where the greater the haemorrhage, the more the transfusion, and the greater the transfusion, the greater the haemorrhage. Application of this philosophy in transplantation saw a very large reduction in the transfusion of blood derivatives without an increase in haemorrhage despite not correcting the abnormal clotting test results. One of the biggest criticisms of this hypothesis is whether maintaining a restrictive liquid policy might favour the onset of post-operation kidney failure, which is why current practice is to use these restrictive systems in moderation. During transplantation we attempt to maintain a restrictive system during hepatic dissection and, from the anhepatic stage, normalize intravascular volume until completion of surgery with a slightly negative liquid balance, thus making NA necessary to maintain correct arterial pressure.

Regarding the intraoperative replacement of blood derivatives, it is important to bear in mind that the efficacy of coagulation prophylaxis has not been demonstrated. Plasma transfusion is reserved for situations with obvious haemorrhage and prothrombin time (PT) below a certain level, in our case 40%. Likewise, correction of fibrinogen or platelets is reserved for situations where levels are below 1g/L and 30x109/L, respectively, with evidence of haemorrhage. The trigger for haemoglobin transfusion is set at approximately 8g/dL.

- **Platelets:** Establish a transfusion trigger of 30,000 platelets. In suboptimal livers, maintain platelet values around >50,000. Replacement dose will be 1 pool of platelets.
- **Fibrinogen:** Always replace when values are below 1 g/L. Between 1 and 1.3 g/L, replace at anaesthetist's judgement. Can be corrected with fibrinogen 4g or cryoprecipitates 2 U/10 kg.
- **Fresh frozen plasma (FFP):** Administer with a PT <20% or INR> 3.00 in the presence of microvascular haemorrhage. Dose 15 ml/kg.
- **RBC:** Intraoperative trigger, Hct 24% or Hb 8 g/dL, on termination of surgery: Hct 27% Hb 9 g/dL.
- **Antifibrinolytics:** Presence of hyperfibrinolysis ROTEM L30, L45, L60 <85. Single bolus of tranexamic acid 10 mg/kg. Except in Budd-Chiari and live donor recipients.
- **Dry patient protocol:** This consists of a restrictive liquid administration policy to maintain a low CVP, using vasoconstrictors where necessary to maintain blood pressure, and diuretics.

2. KIDNEY

2.1 Anaesthesia in kidney transplant

Each age group of kidney transplant patients, from paediatric to elderly, requires a different evaluation and appropriate anaesthesia protocol.

A patient who requires a kidney transplant has stage 5 chronic kidney disease and is receiving substitution treatment, which may be peritoneal dialysis or haemodialysis. In some cases of live donor transplant, the patient may be in stage 4 and not yet receiving dialysis, so the transplant preemptive. Some patients may present residual diuresis that should be evaluated for loss with a view to immediate post-operation diuresis control.

Length of time on dialysis is one of the worst prognostic factors for graft and patient survival.

Anaesthetic control of the patient during kidney transplant is conditioned by donor type:

- Living donor. A scheduled transplant enables operation in optimum conditions.
- Brain-dead deceased donor, with or without kidney risk factors. Emergency transplant when an organ becomes available.
- Heart failure donor. Emergency transplant where delayed graft functioning may occur.

In some living donor cases patients may be ABO incompatible. In these cases, a cross-over transplant may be performed, or the patient may be offered an ABO incompatible transplant. In the latter case, the patient is conditioned with specific immunoadsorption sessions or plasma exchange (plasmapheresis) before the transplant with administration of polyclonal immunoglobulin, such as a treatment with rituximab (monoclonal antibody anti-CD20).

2.2 Preoperative stage

Heart and kidney disease are associated and may negatively influence both organ functions. Many patients present high blood pressure treated with one or several drugs and associated hypertensive heart disease, frequently hypertrophic cardiopathy. Patients with an evolution of many years may present chronic hypotension. Intravascular volume and the presence of hypertrophic cardiomyopathy or dilated cardiopathy must be evaluated.

Ischaemic cardiopathy risk factors evaluated:

- Patients >60 years.
- Diabetes.
- History of coronary disease.
- Presence of cardiovascular risk factors (HBP, dyslipidaemia, diabetes, smoking, obesity, sedentary lifestyle, stress).

Examinations to be performed: Echocardiogram, cardiac stress test and carotid Doppler. If any abnormalities are found, other examinations will be considered.

An aortoiliac CT angiography, conducted as a surgical preoperative study, also informs us about the degree of arteriopathy at this level.

Functional respiratory tests are performed in case a respiratory pathology presents itself and presence of biological risk is studied (HVC, HVB, HIV).

The most common pulmonary abnormality is in relation to the volume overload that these patients may present.

Metabolic alterations are varied. The possible presence of hyperpotassaemia and metabolic acidosis can occur. An electrolyte panel and acid-base balance should be determined on the patient's admission for transplant.

Anaemia accompanies advanced chronic kidney insufficiency due to a reduction in erythropoietin synthesis. Patients are treated with erythropoietin, which achieves haemoglobin figures within a normal range. The presence of thrombocytopathy has been described, however, this does not usually have consequences during transplantation.

When a patient is admitted for transplant, an urgent preoperative evaluation is necessary, and blood must be ordered. Potassium values of 5.5 mmol/L or higher indicate that dialysis prior to transplant should be considered.

2.3 Intraoperative management

Kidney failure alters the pharmacokinetics and pharmacodynamics of most drugs, particularly those that are eliminated via the kidneys. Habitually used drugs include short-action benzodiazepines like midazolam, hypnotics like propofol and pentothal, morphinoids like fentanyl. Muscle relaxants present kidney elimination of the drug or metabolites, so their effect is prolonged. Cisatracurium, which metabolises in plasma, may be used and its metabolite, which is eliminated via the kidney, has no action. Inhalants may have side effects on the kidney. Desflurane has a safer pattern, although sevoflurane use has been described as safe.

Although regional anaesthesia has been described in kidney transplants, general anaesthesia is routine. Epidural catheterisation and combined anaesthesia may be used provided patient medication or coagulation abnormalities do not contraindicate it.

It is highly advisable to continuously monitor CVP during kidney transplant. Although its good correlation with the patient's volemic status is debatable, it always correlates when very high or very low values present. Invasive blood pressure (IBP) monitoring is useful but not essential in young patients with a short evolution of kidney disease. For patients with cardiac abnormalities (ventricular dysfunction, valvopathies or pulmonary hypertension) the pulmonary artery catheter may be useful with mixed thermodilution and venous saturation. However, in recent years, the use of non-invasive monitoring systems like PiCCO®, LiDCO® or Vigileo® has become common. These systems lack sufficient reliability and are greatly surpassed by transoesophageal echocardiogram (TEE).

Haemodynamic monitoring is important due to intraoperative volume expansion performed to increase kidney blood flow and improve graft function. The initial aim is to achieve a CVP over 7-10 mmHg during surgery.

Volume expansion is generally performed with saline serum at 0.9% to prevent an increase in plasmatic potassium, although reports exist of the use of Ringer lactate and plasmalyte without the onset of secondary hyperkalaemia.

Another objective is to maintain a normal pressure status or slight hypertension both intraoperatively and in the immediate postoperative period. To do so it may be necessary to use vasoactive drugs. After ensuring that the patient is not hypovolemic, dopamine or noradrenaline are used for this.

To achieve better graft functions, all groups usually use dopamine, mannitol and furosemide. Although there is no clear evidence these measures are still used by the majority of groups.

When colloid is necessary, albumin is the colloid of choice. Synthetic colloids are associated with changes in coagulation and kidney damage, for which reason they should be excluded. However, reports exist of the use of hydroxyethyl starch (HES) in both kidney transplant and donation.

Transfusion of RBC used to be necessary in kidney transplants, however, it is currently often unnecessary during surgery due to prior treatment with erythropoietin. Nevertheless, non-RBC administration during hospital stay cannot be guaranteed. Routine administration of other blood products is unnecessary.

The administration of immunosuppression medication partly coincides with the surgical intervention. These drugs should be administered in accordance with the corresponding administration dilutions and rhythms, and there should be monitoring for the onset of side effects.

These transplant patients are predisposed to presenting metabolic acidosis that should be corrected when pH figures go below 7.20.

2.4 Postoperative stage

Kidney transplant surgery does not require routine intensive care, although monitoring of intravascular volume, urine output and hydric balance during the first hours is necessary. Therefore, it is advisable to admit patients for monitoring to a unit on day one.

Postoperative pain can be well controlled with peridural analgesia in continuous perfusion or PCA with local anaesthetics and morphinoids. Parenteral morphinoid administration may be an alternative. Use of non-steroid anti-inflammatories should be avoided given their adverse effects on kidney function.

3. PANCREAS

3.1 Pancreas-kidney transplant

A pancreas transplant is indicated in type I diabetes, and usually performed when the patient develops stage 5 chronic kidney disease. This is why most pancreas transplants are simultaneous with kidney transplants; however, it is also possible to perform a pancreas transplant after a kidney transplant and occasionally a pancreas transplant alone.

3.2 Preoperative stage

The onset of all disease complications usually affects patients who have a long diabetic evolution; however, the progression of kidney disease is shorter.

Diabetes is the main cause of cardiovascular disease. Many patients have presented or will present cardiac events, mainly ischaemic cardiopathy, in the form of angina or infarction and there is a high incidence of sudden cardiac death. A systemic study should be conducted to detect comorbidity.

- Functional respiratory tests.
- Aortoiliac CT angiography.
- Echocardiograph.
- Cardiac stress test: Myocardial SPECT is currently done with ^{99m}TcMAA and dipyridamole.
- Should there be symptoms or if the stress test is positive, cardiac catheterization should be performed.

The presence of vegetative dysautonomia, which may hinder haemodynamic stability during the intraoperative period, should be evaluated.

Likewise, the patient's airway should be evaluated bearing in mind the increase in frequency of airway difficulties.

3.3 Intraoperative management

The presence of gastroparesis secondary to neuropathy is habitual, so fast anaesthetic induction sequences should be used.

If transplantation is performed simultaneous to a kidney transplant all other considerations are similar to kidney transplantation.

Possible preoperative anaemia, intraoperative bleeding and the possibility of the patient suffering an ischaemic cardiopathy make a non-cautious approach to RBC replacement necessary. Routine administration of other blood products is unnecessary.

One of the most frequent complications is vascular thrombosis, particularly venous thrombosis. This fact obliges prophylaxis with low molecular weight heparin and acetylsalicylic acid. For the same reason, the reduction of blood volume and cardiac output should be avoided. Hypotension is frequent after reperfusion of a pancreatic graft which, in the absence of hypovolemia, responds to low doses of noradrenaline. There should be haemodynamic monitoring and, in a kidney transplant, monitoring of cardiac output is also advisable for greater precision in the prevention of haemodynamic abnormalities.

Administration of colloids in addition to crystalloids is necessary to maintain blood volume. Use of colloids should be limited to albumin, excluding the use of synthetic colloids that may harm kidney function.

Strict glycaemic control must be maintained, endeavouring to keep glycaemia between 100 and 150 mg/dL with glucose and insulin administration, both in perfusion. It is usually sufficient to perform a glycaemia timetable determination via point of care. Once glycaemia is normalised and pancreas reperfused, insulin administration is no longer necessary.

3.4 Postoperative management

On termination of the intervention, mechanical ventilation is necessary and may be removed once the patient has a normal temperature, is haemodynamically stable and the absence of bleeding has been verified.

Peridural analgesia with local anaesthetic infusion and Fentanest is a good alternative. Failing that, opioids via parenteral catheter may be used.

4. ANAESTHESIA IN PEDIATRIC TRANSPLANT RECIPIENTS

Solid organ transplant in the paediatric patient has shown to be an efficient treatment for terminal insufficiency of some organs. Acceptable percentages of complications and survival rates are currently published which are sometimes more positive than for solid organ transplant in adults. The approach to the paediatric patient begins with the premise that a child is not a "small-sized adult". Each child presents with their own anatomical, physiological, physiopathological and psychological characteristics that are very different from that of an adult.

Generalities of anaesthetic technique in a child patient

The main characteristics of the paediatric patient are their growth and maturity until reaching adulthood. The term paediatric includes children up to 18 years of age (UNICEF, and WHO up to 19), and depending on age, a different terminology is used, i.e., newborn (1 to 28 days), infant (up to 1 year), child (up to 10) and adolescent (from 10 to 19). Morphologically, a child presents a larger skull caused by the development of the brain in relation to face and trunk. Regarding internal organs, there is also a visceromegaly at the expense of the liver and spleen. The greater body surface means a greater loss of heat and different pharmacological posology.

Among the anatomical differences the anaesthetist must take into account to prevent intubation problems are the characteristics of the paediatric airway. In the early ages of a child's life, it is essential to consider a nasal respirator adapted so the child can be fed. A child presents a large tongue, a U-shaped epiglottis and a more anterior location of the glottis. The larynx is conical, the narrowest part being the cricoid cartilage below the vocal cords. As a child grows, the larynx adopts the anatomical cylindrical characteristics of an adult larynx at around 10 years of age and the glottis becomes the narrowest part. The smaller calibre of the upper airway and tendency to oedema and mucosa lesion means a paediatric anaesthetist usually uses endotracheal tubes without a cuff.

This involves a greater extubation risk, considering nasotracheal intubation in procedures involving prolonged intubation and mechanical ventilation. Growth is a characteristic of paediatric age and involves elevated metabolic rates, obtained from a high cardiac output and oxygen consumption, reduced residual pulmonary capacity and an airway closure volume close to vital capacity. Consequently, paediatric patients present a greater tendency to hypoxemia that triggers bradycardia. The immaturity of the different systems and tissues should be considered in the physiological parameters of the different ages (e.g., haemoglobin figures, clotting factors, proteins, etc.), pharmacological dosage and lower functional reserve which may lead to failure.

Generalities of paediatric transplant

The aetiologies causing terminal organ failure among these patients are different from an adult's and also vary between the different age groups. A high percentage are secondary to the congenital pathology of metabolic defects, which frequently affect organs or systems other than the organ to be transplanted and involve more complex anaesthetic management.

Terminal organ failure alters the synthetic, purification and hormonal functions of these patients. Moreover, the deposit of toxic substances will irreversibly affect cognitive development, which together with the greater life expectancy at paediatric age means transplantation and optimal graft are a priority. The undernourishment which paediatric recipients prematurely suffer worsens the prognosis of the procedure. The paediatric patient's smaller size means greater difficulty in finding appropriate organs. It also means an increase in anaesthetic and surgical technical difficulties, high transfusion needs, and a greater incidence of complications. This is the transplant group that has most benefited from advances in surgical techniques, reduction techniques, live donors and the application of new anaesthetic knowledge in transplantation. Paediatric donors are scarce, and a large proportion of grafts come from adult donors. The disproportion between graft and recipient size is common in the cases of the heart and kidneys, where there is no possibility of surgical reduction. Thus, a paediatric recipient must adapt to the adult's physiology to ensure graft survival.

The immaturity of the immune system means greater graft tolerance. However, immunosuppression treatments in paediatric patients imply specific long-term repercussions. Survival percentages are high, representing efficient therapy for terminal organ failure.

The paediatric patient usually requires anaesthetic procedures from diagnosis to therapeutic interventions. The anaesthetist must be familiar with the physiopathology of the terminal organ, its systemic repercussions, as well as the considerations and complications for the transplanted patient. For a child, the preparation for a liver transplant procedure requires more time since vascular access can be difficult due to size, thrombosis or prior venotomies. Likewise, surgical dissection is more laborious due to previous surgeries.

4.1 Anaesthetic approach to paediatric liver transplant recipients

Paediatric liver transplantation patient survival rates are close to 90% at 10 years, although there are short-term complications to consider.

Unfortunately, the number of patients requiring transplant exceeds available organs, and the United Network for Organ Sharing (UNOS) estimates waiting list mortality at 17%. To reduce waiting list mortality, criteria were established to assign organs according to recipient severity, i.e., MELD for adults and Paediatric End-Stage Liver Disease (PELD), 2002, for children under the age of 12 years. MELD assigns a classification obtained by applying a mathematical formula based on creatinine levels, clotting according to international normalized ratio (INR), bilirubin and others. PELD includes albumin levels, growth delay and patient age but excludes creatinine levels.

The percentage of paediatric donors is relatively low and there is frequently a disproportion with adult grafts. Paediatric recipients have benefited from surgical reduction techniques, transplant, lobe transplant, split (one divided organ for two recipients) and live donors. Paediatric transplants represent 12.5 % of all liver transplants.

1. Aetiology

Acute child liver diseases usually have a neonatal onset and a rapid progression, which explains why half the recipients are breastfed or under the age of two.

A) Cholestatic disease: The most frequent reason for liver transplants in children is biliary atresia (58%), which is neonatal entity of unknown origin evolving towards progressive fibrosis of the extrahepatic bile duct. Initially, an attempt to prevent progression of the disease is made in infants by

performing a hepatoportoenterostomy or Kasai procedure. At the time of transplant, they present the surgical difficulties of a preliminary surgery and have higher transfusion requirements. Other causes of cholestasis are bile duct hypoplasia, intrahepatic cholestasis or Alagille's disease with the involvement of other organs, among which associated congenital cardiomyopathy is frequent.

B) Metabolic diseases, with primary hepatic involvement (Wilson's disease, α1-AT deficit, tyrosinemia, cystic fibrosis, or primary non-hepatic diseases (hyperoxaluria, congenital hyperlipidaemia) for which a liver transplant is curative.

C) Sudden liver failure, 23%, secondary to toxins, infectious, autoimmune or idiopathic.

D) Liver tumours (5%).

E) Miscellaneous (parenteral nutrition, etc.).

2. The physiopathology of hepatic failure. Multi-organ system repercussions

A) Cardiovascular system

A hyperdynamic status (increased cardiac output, reduction of systemic vascular resistance, elevated mixed venous saturation) that is secondary to non-detoxified substances and has a vasodilator effect, and the presence of portosystemic collateral. Extreme precaution is necessary due to the risk of paradoxical embolism.

B) Respiratory system

A tendency to hypoxemia of different origins exists, as does a presence of intrapulmonary arteriovenous communications, pulmonary vasoconstriction, a reduction of functional reserve capacity (FRC) due to compression by ascites and organomegaly. The presence of hepato-pulmonary syndrome and pulmonary hypertension has fewer incidences than in adults and a better posttransplant resolution, but nonetheless must be considered.

C) Renal system

Evaluate pre-kidney failure, hepato-renal syndrome and the presence of acute tubular necrosis.

D) Nervous system

Encephalopathy is a neuropsychiatric syndrome associated with liver dysfunction which is not always clinically obvious in infants and small children and is likewise difficult to differentiate from other causes (sepsis, dyselectrolytemia, hypoglycaemia, anxiety). Its classification presents differences compared to older children and adults. To date, the role of other neurological function monitors is not clear in the detection of encephalopathy.

Brain oedema is more frequent in acute liver failure and advanced encephalopathies. Its diagnosis is difficult at early stages, and it may cause a hypoxic and ischaemic or herniated brain lesion. There is controversy about intracranial pressure (ICP) monitoring due to the serious associated complications in patients with coagulopathy.

E) Hepatic involvement

i. Clotting abnormalities: These are due to a reduction in hepatic synthesis and the degradation of both pro- and anti-coagulating clotting factors. A fragile balance is maintained which may incline towards bleeding or the onset of thrombotic phenomena. Monitoring of clotting is limited to classical laboratory tests (prothrombin, PTT/INR), and dynamic determination of the clotting condition is required. Equipment now exists to perform thromboelastograms based on the response of viscoelastic capacities in clot formation and its degradation, thus offering a more global vision of the different elements that interact in clotting. The drop in hepatic synthesis factors I, II, V, VII, IX, X and pro-coagulants (AT III, proteins S and C,

and others) is revealed, as is the increase in factor VIII levels. Thrombocytopenia is frequent due to hypersplenism, antibodies, and so on.

Table 1. Hepatic transplant stages

Stage	Surgical procedure	Repercussion
Pre-anhepatic stage dissection	» Bilateral subcostal incision » Hepatic pedicle dissection » Graft preparation	» Hypotension » Hypothermia » Glucose homeostasis » Blood losses and liquids (ascites) » High fluid therapy and transfusion requirements
Anhepatic stage	» Vascular and bile duct dissection and section » Vascular anastomoses	» Cardiovascular alterations (avoid increases in CVP) » Hypoxemia » Metabolic alterations
Neohepatic stage	» Reperfusion and haemostasis » Hepatic artery anastomosis » Reconstruction of bile duct and Roux-en-Y » Incision closure (consider deferred closure)	» Reperfusion syndrome » Careful liquid replacement » Hct <30%

ii. Changes in glucose homeostasis: On reduction of glycogen deposits, there is alteration of neo-glycogenesis, insulin resistance shows a tendency towards hypoglycaemia aggravated by acute liver failure. The younger the child, the greater the tendency to hypoglycaemia and the greater central neurological involvement (seizure, haemorrhage, permanent brain lesion) a child cannot tolerate prolonged fasting, and serum therapy with glucose and ions is compulsory.

iii. Due to the reduction in protein synthesis, oncotic pressure reduces and the free active drug action increases.

iv. Changes in basic-acid balance and difficult to control electrolytes: sodium, potassium, calcium, phosphorus and magnesium. Pre-operation hyperkalaemia and hypocalcaemia are more frequent than in adults and should be treated.

F) Liver transplant stages. A liver transplant has 3 clearly defined stages, each with its own peculiarities.

G) Monitoring

From less to more aggressive as anaesthesia deepens. Central and peripheral venous and arterial vascular accesses should be in the upper territory since abdominal aorta and vena cava inferior clamping could occur during the surgical procedure.

- Haemodynamics: EKG, invasive arterial pressure, CVP, mixed venous saturation, TEE, cardiac output via thermodilution and wave pulse analysis.
- Ventilation/Oxygenation: ventilation, anaesthetic gases, pulse oximetry, precordial or oesophageal stethoscope.
- Catheters: urinary output, bladder catheter, core temperature.
- Neurological monitoring: Electrical brain activity with bispectral index (BIS), regional brain oxygen saturation (INVOS). Special situations, transcranial Doppler, and intracranial pressure (ICP).
- Laboratory: Basic-acid balance, electrolyte panel, clotting, complete blood count, glucose, kidney function and thromboelastography, ammonium.

H) Anaesthetic management

Consider the possibility of a full stomach and perform RIS on tracheal intubation.

Both the drugs and the anaesthetic techniques are similar to those used for adults. The usual hypnotics are propofol and pentobarbital, reserving ketamine and etomidate for haemodynamic instability. Maintenance is via fentanyl perfusion, non-depolarising muscle relaxant (cisatracurium) and inhaled halogenated agents (isoflurane, sevoflurane) with midazolam perfusion on certain occasions.

It is essential to have fluid therapy, blood derivatives and vasoactive drugs ready since the patient may suddenly become destabilized at any time during the procedure.

In fact, the cirrhotic patient is considered to present alterations in the regional distribution of blood volume, with accumulation in the splanchnic area. Volume overloads do not produce an increase in central or arterial volume but an increase in non-central volume, the splanchnic area, which in turn increases hepatic congestion and hydrostatic venous pressure, augmenting the risk of haemorrhage. Common sense should be used for fluid therapy and transfusion, with administration of vasoactive drugs in the event of haemodynamic instability.

Patients with evolved hepatic disease suffer kidney failure and an increase in ammonemia. The use of extra-renal purification systems during transplant enables better haemodynamic and metabolic control, likewise excellent survival rates for patient and graft.

6. Repercussions of modified surgical techniques

The liver graft of the paediatric recipient is frequently split (split, reduced graft, live donor), which means greater technical surgical difficulty, possible complications, a longer procedure duration and the need for transfusion.

The standard surgical technique is “piggy-back”, in which there is partial clamping of the lower cava and the graft suprahepatic veins are anastomosed en bloc to the recipient’s lower suprahepatic cava. This reduces both surgical time and the risk of haemorrhage, as well as being haemodynamically better tolerated by the patient. However, in some centres and depending on the anastomosis to be performed sometimes a full clamping of cava is necessary.

Collateral circulation developed by cirrhotic patient facilitates haemodynamic tolerance to vascular clamping compared to non-cirrhotic patients (metabolopathy, acute liver failure, tumours).

7. Special situations in a liver transplant

A. Coagulopathy: Different factors cause coagulopathy. The fragile clotting balance of these patients and the risk of dilution coagulopathy mean that the aims of factor transfusions are less clear than RBC levels. Restrictive strategies are used to maintain CVP, enabling a reduction of bleeding risk secondary to overload of the splanchnic area and less dilution of plasmatic clotting factors. It is recommendable to evaluate each case individually when administering pro-clotting factors or prophylactic plasma transfusion prior to a procedure. In a paediatric transplant, the administration of factor concentrates (prothrombin complex, antithrombin III, fibrinogen, FVIIr) instead of plasma to prevent hypervolemia is common.

B. Bleeding: Liver transplantation is associated with a high surgical bleeding risk. This is higher in paediatric transplants due to the existence of previous abdominal interventions and the small size of the patient. It is important to avoid the risks of over-transfusion (liquid overload, vascular thrombosis inherent to the transfusion). It is, therefore, important to consider estimated blood loss and have transfusion goals: a) Haemoglobin 8-9 g/dl, Haematocrit 25-28%, b) Platelets >50x10^3/mL, c) Prothrombin T. <20 sec, d). Fibrinogen >100 mg/dl.

C. Hypothermia: Related to clotting abnormalities, pharmacological effects and haemodynamic instability, etc., the larger the body surface of the paediatric patient, the more susceptible it is to heat loss. This makes it important to have active patient warming systems, liquids, and ventilation to prevent exposure, in addition to monitoring systems. Reperfusion is usually the most problematic moment.

D. Cardiovascular alterations: Haemodynamic abnormalities secondary to surgical manipulations of the liver transplant are usually better tolerated in the paediatric patient, who has a better cardiovascular reserve. Although they may occur at any stage, clamping in the anhepatic stage is better tolerated in patients with portal hypertension (pathologies with cholestasis) than those without collateral circulation (metabolic impacts). The reperfusion syndrome triggered with graft perfusion is due to low temperature blood with ischaemia and preservation products entering into blood circulation. The onset comes with hypotension, arrhythmia, bradycardia, and occasionally requires RCP. Lavage prior to graft is important, as is recipient preparation, stabilizing the acid-base balance, hypocalcaemia, hyperpotassaemia, haemoglobin and temperature prior to unclamping. Some groups administer prophylactically calcium chloride and inotropes.

E. Kidney involvement: It may be necessary to perform the transplant with an extra-renal purifying system.

F. Changes in the acid-base balance: Electrolytes and glucose are usually more frequent and extreme, secondary to the small size and large blood volume replacement paediatric patients require. Frequently hypocalcaemia, hypomagnesaemia, hypo- or hyper-potassemia, sodium, phosphate and chloride alterations, some of which cause cardiovascular changes and life-threatening arrhythmias.

Premature death prediction factors in paediatric liver transplant include pre-reperfusion metabolic acidosis, hyperglycaemia and hyperlactacidemia post-reperfusion, worsened by bleeding and massive transfusion, essentially of platelets.

G. Encephalopathy: This is one of the most worrying symptoms when clamping is aggraveted by hyponatremia. Brain flows benefit from the administration of hypertonic solutions during the anhepatic stage. During surgery on a patient with endocranial hypertension, measures of proven efficacy in the ICU should be considered. These include hydric restriction, oxygen saturation over 95%, avoiding hypotension, moderate hypothermia, hyperventilation and head elevation. Continuous therapy of renal replacement reduces levels of ammoniemia, while control of uraemia and blood volume levels improve symptoms. Evaluate the risks/benefits of ICP monitoring in patients with coagulopathy.

8. Complications

The percentage of complications is higher among paediatric patients.

» The most dreaded complication (between 10-26%) is hepatic artery thrombosis that requires re-intervention, frequently leading to graft loss if it occurs within the first 2 weeks of transplant. Most common in anastomosis under 3 mm are:

» Portal vein thrombosis.

» Primary dysfunction of graft.

» Bile duct complications (10–30%), associated with prolonged preservation time, ischaemia or surgical technique.

» Bleeding requiring surgical revision.

» Infections.

» Higher incidence of retransplant (10-20%).

1. Long-term transplant repercussions

» Impact on kidney function secondary to nephrotoxicity caused by immunosuppression.

» Cardiovascular impact, progression of atherosclerosis due to elevation of lipids and HBP.

» Central nervous system toxicity, tacrolimus convulsions.

» PTLD, more frequent from 2 years posttransplant and related to EVB virus infections.

» Delayed growth.

» Impact on school performance.

4.2 Anaesthetic approach to paediatric kidney transplant recipients

The paediatric kidney transplant recipient presents higher survival, cognitive development and growth rates than those on dialysis. Thus, paediatric kidney transplant is necessary.

1. The physiopathology of kidney failure

Failure occurs in purification, liquid balance and hormonal synthesis (erythropoietin, aldosterone, and renin).

A. Cardiovascular: Cardiac output increases in kidney failure, hypertension is common, as are pericardial effusion and congestive heart insufficiency, which may be associated to dysrhythmias. Increased coronary arthropathy.

B. Growth: Delay is more intense when younger, osteoporosis.

C. Haematological: Chronic anaemia, platelet function abnormalities.

D. Neurological: Cognitive delay, hyperactivity, CNS depression, PNS dysautonomia, prolongation of non-depolarizing muscle relaxants.

E. Volume overload: Electrolytic alterations: hypocalcaemia, hyperpotassaemia, hyperphosphatemia. Metabolic acidosis.

F. Gastrointestinal: Reflux, gastric evacuation delay, hypoproteinaemia.

2. Aetiology

Chronic kidney failure is not common in the paediatric population. In infants and small children, kidney failure is due to congenital or anatomical alterations (kidney dysplasia/aplasia, obstructive uropathy, bladder alterations).

Among older children it is usually secondary to metabolic or immunological diseases and has less recurrence than in adults.

3. Surgical technique

In children weighing over 20 kg the surgical technique is extra-peritoneal and similar to that of an adult. In recipients under this weight, anastomosis is performed directly on the aorta and vena cava.

A large part of the recipient's cardiac output is taken towards the graft. In small children, the onset of thrombosis and primary graft failure are more frequent.

4. Monitoring

Standard haemodynamic and ventilation monitoring including bladder and gastric catheter, temperature control, anaesthetic depth (BIS). It is also advisable to monitor muscle relaxation. If you are experienced, a transthoracic echocardiogram (TTE) is useful to evaluate ventricular function and blood volume.

There should be a central venous insertion in the upper vena cava to control CVP, serial analyses, administration of irritant and vasoactive drugs. Direct arterial monitoring is considered in infants receiving an adult graft or recipients in whom haemodynamic control is difficult.

Large calibre angio-catheters should be available in the upper territory avoiding arterio-venous fistulas.

5. Anaesthetic management

A. Preoperative evaluation

Consider hypertensive treatment and ion supply. There should be a recent echocardiogram and analysis, special attention to electrolyte panel, basic-acid state, level of anaemia, and clotting state. Haemodialysis without heparin prior to operation.

B. Induction

The anaesthetist should consider the haemodynamic alterations these patients suffer on anaesthetic induction. Hypotension via prior dialysis and reduced blood volume with involvement of the autonomic system, such as base hypertension and hypertensive peaks triggered by airflow manipulation, which may be difficult to control. The operating theatre should have fluids, vasoactive drugs and hypotensive medication available.

C. Anaesthetic management

In paediatrics, general anaesthesia is performed with controlled ventilation. For post-operation analgesia, a lumbar epidural or a peri-incisional catheter are used, inserted by surgeon on closing abdominal fascia.

D. Ventilation

In managing airflow, consider the broncho-aspiration risks involved as these patients have slow gastric evacuation.

Maintain normocapnic ventilation, as hyperventilation causes vasoconstriction that reduces oxygen availability in tissues, whereas hypoventilation aggravates acidosis.

E. Fluid-therapy

Requires very careful management with personalized supplies of ion and bicarbonate, without potassium. Initial subjacent hypovolemia should be corrected. The anaesthetist must be aware that the standard criteria for blood volume replacement (BP, HR, CVP, diuresis and basic-acid balance) are limited in these patients.

6. Vascular unclamping

For graft survival it is important that CVP prior to vascular unclamping be high, between 8 and 12 cm of H_2O, and up to 15–20 cm H_2O in infants with an adult graft. With graft reperfusion, preservation products are released which reduce peripheral vascular resistance, intravascular volume, acidosis and potential symptoms of serum hyper potassium such as arrhythmias requiring treatment. Anastomosis bleeding may aggravate these symptoms.

To ensure graft perfusion, filling pressures should be kept high until correct diuresis is established. Initially, there is a phase of polyuria without concentration capacity that requires a large volume of crystalloid infusion. Consider the administration of diuretics. When the graft is adult, adult systolic arterial pressures and physiological means must be kept, which may mean haemodynamic overload in the paediatric patient, aggressive volume replacement and the need to administer inotropes. There is an increased risk of heart failure and pulmonary oedema.

In some cases, controlled ventilation maintained during the immediate postoperative period in the ICU and deferred abdomen closure may be considered to prevent an increase in abdominal compartment pressure, which could compromise the vascular flow of the new organ.

7. Transfusion

Haemoglobin levels must be kept relatively high before reperfusion and forestall the graft "stealing" the recipient's cardiac output.

An adult kidney requires a volume of 300 cc for reperfusion, which may represent 20 to 50% of blood volume. In recipients <15 kg, perform prophylactic transfusion.

8. Immunosuppression

Immunosuppression guidelines continue after anaesthetic induction. Protocols vary according to patient, whether this is a re-transplantation, or other factors which may facilitate rejection.

The anaesthetist must consider the adverse effects of administering immunosuppression, like fever, hypotension, rash, and so on. These drugs should be administered slowly, making adjustments to perfusion times when unclamping.

9. Anti-thrombotic prophylaxis

The application of this protocol has improved organ survival, and is divided into three groups according to thrombotic risk, with different posttransplant guidelines:

- Low risk (first transplant, >15 kg), prophylaxis not required.
- Moderate risk (retransplant, <15 kg, live donor), begin aspirin (ASA).
- High risk (thrombophilia, immunological disease), administer sodium heparin.

10. Complications

The most frequent complications in paediatric recipients and paediatric grafts are:

» Delay in graft function (dialysis needed during first week of intervention, incidence is less in live donor grafts than cadaver donors).

» Thrombosis is more frequent in the paediatric recipient (0.3-6% NAPRTCS).

» Long term complications (coronary arteriopathy, diabetes, etc.).

4.3 Anaesthetic approach to the lung transplant recipients

Paediatric lung transplants represent 5% of lung transplants. Although indications are growing in adults, figures for paediatric patients are stable. In Spain, survival figures for paediatric transplants are between 65 and 70% at 5 years and 62% at 8 years. These rates are higher in small children due to possible immunological tolerance of the graft secondary to the immaturity of their immune system.

One of the most difficult aspects is the decision about when to put a paediatric patient a waiting list. The reason for this is the rarity of many chronic child lung diseases, for which it is difficult to predict survival. The new drugs available to treat primary pulmonary hypertension have enabled transplant to be postponed in many cases.

The vast majority of paediatric lung transplants are bi-pulmonary, and in our centre, the Vall d'Hebron hospital, 85% require extracorporeal circulation (ECC), with its consequent deleterious effects.

4.3.1 Aetiology

The most frequent indications for paediatric lung transplantation are cystic fibrosis (CF) (56%) and pulmonary hypertension, which may be idiopathic (10%) or related to congenital cardiopathies (5%). Distribution varies between the different ages. Thus, CF is typical of adolescence whereas interstitial pneumopathy is more common among infants.

These aetiological differences by age involve different anaesthetic considerations. For infants, preoperative mechanical ventilation is usually required or other support systems, i.e., high frequency oscillatory ventilation (HFOV) or extracorporeal life support (ECLS) which limit vascular access and hinder transfer to the operating theatre. Among adolescents with CF there are associated co-morbidities: diabetes, pancreas failure, growth delay, polymedication, etc., and chronic respiratory over-infection. It is compulsory to apply techniques that take extra care of airway management and prevent graft contamination, as is administering specific antibiotic therapy.

4.3.2 Donor organ

The organ shortage problem is more significant in lung transplantation since ABO compatibility is a requirement as is size compatibility between the donor and the recipient. A lung that is too large for recipient's chest cavity may cause atelectasis, distortion of airways or heart obstruction.

On the other hand, a lung that is too small leads to pulmonary hyperexpansion and impaired pulmonary mechanics. To calculate the donor and recipient's theoretical lung volume, equations based on height, age and sex are used. Organs between 10-15% of theoretical values are acceptable.

4.3.3 Surgical technique

A sequential bilateral lung transplant is usually performed using a "clamshell" incision (bilateral anterior thoracotomy) to facilitate both the approach of pulmonary hila and cannulation for cardiopulmonary bypass (CPB). Telescoped bronchial anastomosis is performed during the surgical

procedure to reduce the risk of stenosis and suture failure. Anastomosis of pulmonary arteries is termino-terminal, occasionally requiring remodelling to adjust to sizes. Graft pulmonary veins are extracted with the donor's left heart atrium, which is anastomosed to the recipient's left atrium. This technique reduces pulmonary vein obstruction, which is a major cause of lung graft failure. Arrhythmia and a reduction in cardiac output are frequent at this stage.

This sequential technique requires selective bronchial intubation and CPB is often required in a first lung implant and more frequently in the second due to hypoxemia, pulmonary hypertension or low cardiac output.

Surgical reduction and lobular transplant techniques have made a larger number of organs available for transplant.

Although not associated with lower survival, possible complications may arise such as bleeding, suture failure and lobular necrosis due to displacement, among others.

Single lung transplants are rare in the paediatric context. Heart-lung transplantation is considered in specific situations.

4.3.4 Anaesthetic management

A. Preoperative evaluation

The status of lung transplant recipients is usually critical. Hypoxemia and hypercapnia may often require supplementary oxygen, controlled ventilation, HFOV or ECLS. In addition, maximum medical treatment, i.e., inhaled, parenteral or oral (inhaled bronchodilators, pulmonary vasodilators, antibiotics, respiratory physiotherapy) may have to be maintained during the intervention.

It is essential to conduct a preoperative evaluation of cardiovascular status, as well as the possible dysfunction of other organs and tissues. Revise right ventricular (RV) function and pulmonary arterial pressure (PAP) via echocardiogram and, if necessary, catheterization. The results of a recent general analysis must be available.

Circulating catecholamine levels are raised by ventilation efforts, and their regulation alters in recipients. Sedation may affect control of ventilation causing severe hypotension, with a lack of response to exogenous catecholamines.

B. Ventilation

The impact of mechanical ventilation on the haemodynamic state will vary according to the underlying pathology causing lung failure. Management of the pulmonary graft should include maintaining a protective ventilation, favouring aspiration of secretions and avoiding lung oedema.

4.3.5 Monitoring

At haemodynamic level, apply the standard monitoring for heart surgery anaesthetic procedure (direct arterial pressure, ECG, cardiac output, pulse oximetry, mixed venous saturation (SvO_2)), ventilation (capnography, respiratory parameters, stethoscope), bladder and gastric catheterization, core temperature control, neurological (BIS, regional brain oxygen saturation (SrO_2C)). To monitor heart function, pulmonary hypertension control, state of vascular sutures and to rule out obstructions of pulmonary veins TEE gives added value. Likewise, it enables diagnosis of embolic phenomena. The pulmonary artery catheter (Swan-Ganz) is not inserted systematically in paediatrics.

Cardiac output measuring systems with pulse wave analysis (PiCCO)® are more useful post-operation with the thorax closed. Intraoperative insertion of a catheter in the pulmonary artery will be for evaluation.

One of the idiosyncrasies of monitoring lung transplantation is double artery insertion at femoral and radial levels which provide more continuous monitoring.

Fibrobronchoscopy facilitates endotracheal tube insertion during ventilation manoeuvres and also serves to evaluate the status of sutures, and blood and secretion aspiration.

4.3.6 Anaesthetic phases in sequential bilateral lung transplant

A. In these patients, the moment of anaesthetic induction is a time of high risk, which may require RCP or immediate entry to CPB. Both should be ready from the time the patient enters the operating theatre. During anaesthetic induction manoeuvres and drugs that aggravate pulmonary hypertension and depress cardiac function should be avoided in favour of broncho-dilation and pulmonary vasodilation. Ketamine causes bronchial reactivity and its effect on vascular pulmonary resistance (VPR) in paediatric patients is a matter of debate.

Nitrous oxide should be avoided due to its effect on VPR and impairment of hypoxic pulmonary vasoconstriction. Opting for low concentration halogenated anaesthetics is useful for producing amnesia and pulmonary vasodilation although it alters hypoxic pulmonary vasoconstriction. It is important to know what effect the different drugs and manoeuvres to be performed may have on pulmonary and systemic vascular resistances.

For CF patients, antibiotic treatment is established according to the sensitivity of colonizing germs, and graft colonization should be prevented. Endovenous or inhaled (tobramycin, amphotericin B) antibiotics are administered.

Selective intense bronchodilator and early pulmonary vasodilator treatment should begin (inhaled nitrous oxide, prostacyclin IV or instilled). Apply immunosuppression treatment that includes methylprednisolone before vascular unclamping.

B. First pneumectomy. This starts with the lung that is in the worst condition. Selective unilateral ventilation is established with single-lumen tube and selective bronchial intubation with a single-lumen or double-lumen tube. Permissive hypercapnia and haemodynamic instability are usual. High airway pressure reduces venous return and also pulmonary blood flow. Adjust ventilation, minimize air entrapment and administer inotropic (noradrenaline, milrinone,) agents to maintain right ventricle function.

Acute hypoxemia, pulmonary hypertension, ventricular failure or acute haemodynamic instability indicate restitution of bilateral ventilation and induction on the CPB.

Pulmonary artery occlusion of a collapsed lung during single-lung ventilation improves with the exchange of gases as ventilation-perfusion improves in the perfused lung, reducing shunt of the collapsed lung. Occlusion of the pulmonary artery causes an increase in PAP and consequently in post-load of the right ventricle. It is important to maintain the correct coronary perfusion, adjusting preload and inotropic support.

C. Vascular unclamping and first lung perfusion, lung inflation should be gentle.

D. Second pneumectomy, careful selective intubation of pulmonary graft is performed with protective ventilation limiting the fraction of inspired oxygen (FiO_2), avoiding peak pressures and elevated plateaus, and establishing positive end exploratory pressure (PEEP) for lymphatic drainage. Serum therapy must be restrictive, carefully start nitrous oxide early with aspiration of secretions avoiding the suture area.

E. Reperfusion syndrome (oedema of the transplanted lungs) is more serious in the second lung since ischaemia time is greater. To prevent re-implantation lesion, start perfusion with PGE1 on releasing the pulmonary artery of the right lung as its vasodilator effect may aggravate haemodynamic instability.

4.3.7 Indications for ECC

Consideration should be given to CPB from the start when simultaneous correction is performed on a heart defect, small children, pulmonary hypertension or in an extreme situation of the recipient's heart and/or pulmonary function. In some centres, paediatric lung transplantation is systematically carried out under ECC. Intercurrent problems such as surgical or electrolytic abnormalities, intubation-ventilation, graft involvement or patient tolerance may mean a possible return to CPB at any time during the transplant.

This consists of CPB at a normal support temperature, maintaining ventilation. Ultrafiltration and modified ultrafiltration (MUF) improve graft function by reducing oedema and mediating inflammation factors. The repercussions of CPB are essentially related to immunity secondary to de-coagulation and greater time consumption.

4.3.8 Complications

The most common immediate post-operation complications are hypoxemia, haemodynamic impairment, haemorrhage and kidney failure. Subsequently, infectious problems and rejection may appear.

1. Bleeding (11% require repeat interventions).
2. Haemodynamic complications are usual immediately posttransplant. Hyperdynamic status, left and/or right ventricular failures are frequent.
3. Airway complications such as stenosis, suture dehiscence, tracheobronchomalacia, vascular complications. Stenosis of pulmonary veins appears as pulmonary oedema. Right pulmonary artery stenosis causes right ventricle overload.
4. Nerve lesions: phrenic nerve lesion, dysphonia, seizures. gastropharyngeal reflux and gastric paresis, arrhythmias, and others.

Among pulmonary complications:

1. Primary graft failure related to preservation, and ischaemia-reperfusion, manifested as hypoxemia.
2. Pulmonary oedema due to reperfusion lesion, CPB, lymphatic drainage impairment, pulmonary venous obstruction, and aggravated by fluid therapy and transfusion.
3. Acute rejection.
4. Pulmonary infection.
5. Obliterating bronchiolitis is a symptom of chronic rejection.

4.4 Anaesthetic approach to paediatric heart transplant recipients

Paediatric transplantation represents 10 to 12.5 % of all heart transplants and its indications are increasing. The demand for organs has meant the development of scaled palliative surgical procedures in certain congenital cardiopathies such as left heart hypoplasia, enabling patient development and postponing the moment of transplant.

Survival is 70–85% at 4 to 5 years, although premature mortality (<30 days posttransplant) is high and the consequence of graft failure, technical factors, infection or multi-organ failure. The onset of late rejection is graft coronary vasculopathy (coronary artery disease).

1. Donor criteria

The difference in weight between the donor and the recipient should be between -20% and +60%, and larger organs are for recipients with pulmonary hypertension (PHT), so the right ventricle has more reserve against elevated post-load. In large organs (ratio >3.0) no differences were observed in ventricular function or ICU stay. If the heart is small, the risk of graft failure increases 50%.

Deferred thorax closure should be considered in the event of large discrepancies in size or haemodynamic instability.

The shortage of donors has led to the implantation of ABO-incompatible grafts, performing sequential plasmapheresis during CPB.

2. Aetiology

Distribution by age is U-shaped and related to aetiology. Congenital heart diseases are more frequent in first year of life. In older children the causes for heart transplantation are cardiomyopathy, as well as and palliated or corrected congenital heart diseases that present dysfunction, i.e., several ventricular failures or untreatable arrhythmias.

Single Fontan types are usually corrected with protein-losing enteropathy. Severe non-reactive pulmonary hypertension indicates heart-lung transplant.

3. Anaesthetic management

A. Preoperative evaluation

Child heart transplant recipients require numerous hospitalizations and anaesthesia. Revision of previous episodes and the patient's current condition are essential. There may be difficulties to vascular accesses due to venotomies or thrombosis. Some patients (stage 1A) are under mechanical support as a bridge to transplantation with ventricular assistance systems (VAD), ECLS, or controlled ventilation and vasoactive support. Previous hospitalizations may lead to increased anxiety, so consider oral, nasal, or endovenous premedication or inhalant induction.

B. Induction

Etomidate or ketamine are usually used in induction but use propofol with caution. Maintenance with perfusions of midazolam and fentanyl, or occasionally with halogenated agents.

C. Physiopathological management

1. Congenital cardiopathies: in the care of these conditions, it is essential to know the pulmonary-to-systemic-flow ratio (Q/S) of each heart disease so as to avoid aggravating the hypoxemia or worsening cardiac output. It is also important to know the effects of the drugs and ventilation on systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) as well as strategies to act on them.

2. Cardiomyopathies:

    1. Dilated cardiomyopathy is the most frequent. Secondary to viral myocarditis, mitochondrial myopathies, extensive infarctions due to an anomalous origin of the coronary artery from the pulmonary artery and cardiomyopathy due to the toxicity of chemotherapy. Avoid bradycardia and increments in post-load PVR.

    2. Hypertrophic cardiomyopathy is associated with mitral valve anomalies. Avoid a drop in

SVR, tachycardia, and preload reduction.

3. Restrictive cardiomyopathy, associated with storage diseases (mucopolysaccharides) is not very common. It affects diastolic function and is accompanied by severe PHT.

D. Monitoring

The standard monitoring for a cardiac surgery is required. Thermo-dilution or pulmonary artery catheters are placed before CPB, or occasionally inserted transthoracically during surgery (catheter in left atrium, pulmonary artery).

TEE is used to evaluate posttransplant heart function and the anastomosis condition of large vessels. Brain oximetry, neurological monitorization with near-infrared spectroscopy (NIRS), anaesthetic depth (BIS), awakenings may occur in patients with bad cardiovascular function due to large adjustments of anaesthetic dosages.

4. Surgical technique

The bicaval technique consists of anastomosis of the donor and recipient's large vessels, and anastomosis of the donor's left atrium onto the left atrium of the recipient's pulmonary veins. This technique reduces the arrhythmias due to scarring from auriculectomies.

The complexity of surgical technique increases in patients with previous heart surgeries, dextrocardia, pulmonary artery hypoplasia or aortic arch and venous return anomalies, which may require correction in hypothermia and cardiac arrest. Donor-recipient size discrepancy forces diaphragmatic plication to give the graft room, or deferred closure of the sternum.

5. Cardiopulmonary bypass

The existence of surgeries and anatomical anomalies means cannulation, normally in the thoracic area, but can also mean femoral cannulation. A CPB is usually performed in moderate hypothermia (25–28°). Ultrafiltration and MUF obtain a reduction in the inflammatory response, besides normalizing volume, electrolytes and haemoglobin. In heart transplants of an incompatible ABO group, exchange transfusion is performed on initiation of CPB. Plasmapheresis is considered when the number of the recipient's antibodies is high.

After CPB monitoring, activated clotting time (ACT), thromboelastography and bleeding control (antifibrinolytics, blood derivatives) are essential. The prolongation of CPB due to a need for correction of anatomical defects, increases the risk of bleeding.

6. Post-cardiopulmonary bypass considerations

A. Unclamping and reheating

1. Ventricular arrhythmias secondary to ischaemia and electrolytic alterations requiring several defibrillations (defibrillation, anti-arrhythmia, magnesium sulphate).
2. Right ventricle failure: Treatments with milrinone, inhaled nitrous acid, levosimendan. When the cardiac graft is unable to support the recipient's right ventricular pacing (RVP), it may temporarily require right ventricular assist devices (VAD) or ECLO.
3. Denervated heart requires stimulation with atrial pacemaker and/or direct -β-adrenergic action drugs (isoproterenol, epinephrine). Does not respond to indirect action drugs like atropine.

B. Ventilation

Establish ventilation strategies that enable RVP reduction and reduce pulmonary hypertension like FiO_2 100%, moderate hypocapnia 32-35 mmHg), avoid atelectasis, elevated airway pressures and auto-PEEP.

C. CPB extraction

1. Administer inotropic support as per hospital protocols (levosimendan).
2. TEE shows biventricular function and the effect of inotropes and vasodilators on vascular resistances, the presence of intracardiac air and the state of the anastomoses. Be cautious with venous obstruction.
3. Reduction of RVP: ventilation strategies and vasodilators (milrinone, prostacyclin, nitrous acid, nitroprusside, nitroglycerine, Ca^{++} antagonists).

D. Posttransplant care

1. The denervated heart does not respond normally to hypotension. Maintain moderate tachycardia (HR 120-150 bpm) and commence vasodilator perfusions which contribute to improving the systolic system and cardiac output.
2. Haemostasis. Administer protamine, platelets, plasma, cryoprecipitates, factor VIIa, fibrinogen. Aggravated in risk groups: ventricular assistance systems, oxygenation with prolonged extracorporeal membrane ECLS and CPB.
3. Fluid therapy must be careful to avoid using solutions with potassium and be guided by left atrium pressure and CVP. Haematocrit targets between 30-35%.
4. Sometimes deferred sternum closure is considered in unstable or small patients.

7. Posttransplant repercussions

A. HBP

B. Hyperlipidaemia (26%)

C. Coronary vasculopathy (11%)

D. Diffuse progressive thickening of epicardial coronary artery intima secondary to the proliferation of smooth muscle cells. Due to cardiac denervation, ischaemic processes are not accompanied by angina pain which hinders diagnosis. Incidence is lower than in adults, particularly in small children.

E. Kidney malfunction (9%)

F. Diabetes (4%)

G. Lymphoproliferative syndromes

CONCLUSIONS

» Solid organ transplants are an efficient therapy in terminal organ failure with excellent survival rates, both in paediatric and adult transplantation, but in infants and small children, who have lower immune reaction to the graft, results might be better.

» Paediatric recipients are those who have benefited most from modifications in surgical techniques and graft reduction. These patients require more technical and derived anaesthesiology techniques, due among other factors to their small size, previous surgeries and concomitant congenital pathology. Volume replacements, electrolytic disorders and transfusion needs are usually more aggressive than in adults.

» However, their haemodynamic tolerance to the transplantation process is usually better. Overall, in transplantation, anaesthesiology and preparation for transplantation are essential to ensure favourable outcomes immediately after transplantation.

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TOPIC 2 - Unit 1

Indications and waiting list

ORGAN TRANSPLANTATION

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INTRODUCTION

Depending on the type of organ transplantation, every transplant patient undergoes a specific type of anaesthesiology and immediate postoperative follow-up.

This unit focuses on the different points that require attention depending on the organ to be transplanted. In addition, it discusses details of waiting list management and urgency listing for certain organs. This matter is important when deciding the best possible approach in terms of the patient's urgency status.

1. KIDNEY TRANSPLANTATION INDICATIONS

The indications for kidney transplant are summarized in Table 1. Nevertheless, not all stage 5 CKD patients can receive a kidney transplantation. In Spain, approximately 20% of patients on dialysis are on the waiting list.

There are contraindications for kidney transplantation which may advise against it (Table 2). Absolute contraindications are very few and present no difficulties; however, in daily clinical practice there are a vast number of intermediate situations that require evaluation on a case-by-case basis.

Table 1. Kidney transplant indications

Indications
Stage 5 chronic disease in dialysis
Stage 5 chronic kidney disease before starting dialysis (preemptive haemodialysis)
Absence of contradiction

Table 2. Kidney transplant contraindications

Absolute contraindications
Immunological (positive CDC crossmatch)
Age >80 years
Active or recent neoplasia
Active infection
Active or recent digestive haemorrhage
Serious organic disease (e. g. severe chronic liver disease or cirrhosis, COPD, non-revascularizable coronary disease or severe dilated cardiomyopathy, neurological disease)
Severe non-revascularizable atherosclerosis
Dementia
Active addiction to toxic substances, drugs or alcohol
Serious psychiatric illness
Extreme obesity (BMI >40 kg/m^2)
Kidney disease with high recurrence risk (primary hyperoxaluria)

Relative contraindications
Immunological (specific donor antibodies, positive cytometry crossmatch)
Age 70-80 years
Neoplasia (as per type and latency period)
Infections (HCV, HIV, HBV)
Organic disease (chronic liver disease, COPD, cardiomyopathy, coronary disease, cerebrovascular disease)
Peripheral atherosclerosis
Psychiatric illnesses
Obesity (BMI 30-40 kg/m^2)
History of drug addiction
Kidney disease with high recurrence risk haemolytic uremic syndrome (HUS)
Extreme obesity (BMI >40 kg/m^2)
Kidney disease with high recurrence risk (primary hyperoxaluria)

1.1 Cardiovascular and pulmonary risk profile

Age

In general terms, there is no age limit for receiving a kidney transplant. The recipient should have a general medical condition that allows the patient to undergo surgery and receive immunosuppressive medication.

Elderly patients have a greater prevalence of vascular calcifications, which may hinder vascular anastomosis, and a greater risk of presenting an organic illness. The assessment of patients over 70 should be case-by-case and requires a complete cardiovascular study.

contraindications are very few and present no difficulties; however, in daily clinical practice there are a vast number of intermediate situations that require evaluation on a case-by-case basis.

Cardiovascular disease

In comparison with the general population, chronic kidney disease patients have a higher risk of presenting a complicated cardiovascular disease. The leading cause of long-term mortality in KT is cardiovascular disease. This makes a thorough assessment of the patient's cardiovascular state a necessity during pre- and posttransplant follow up.

An acute or recent heart disease or condition (myocardial infarction, angina, stent or coronary bypass, heart failure and severe valvular heart disease) may be a contraindication to receive a KT. A previous history of ischaemic heart disease is not an absolute contraindication but will require a meticulous cardiovascular evaluation. (Figure 1).

A recent history of cerebrovascular disease (stroke, brain haemorrhage, transient ischaemic attack, subarachnoid haemorrhage) is an absolute contraindication, and an individualised waiting period should be established before reconsidering inclusion on the KT waiting list. A history of previous cerebrovascular disease requires a thorough individual assessment (ultrasound of supra-aortic trunks, brain CT or MRI, neurological assessment).

Patients with hepatorenal polycystic disease, a family history of intracranial aneurysms or prior subarachnoid haemorrhage should undergo a brain computed tomography angiography (CTA) and neurological assessment.

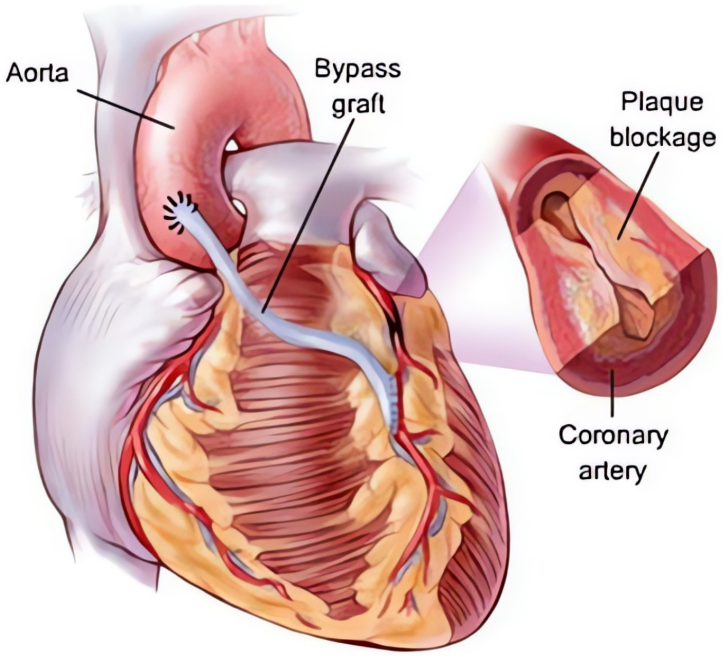

Figure 1. Pretransplant treatment of coronary artery disease risk profile.

Peripheral atherosclerosis

Symptomatic peripheral atherosclerosis or abdominal aortic aneurysm with surgical criteria should be carefully assessed before the transplant. Treatment is necessary (angioplasty, stent, vascular prosthesis or endoprosthesis) before reconsidering inclusion on the waiting list.

In some centres, if there is severe peripheral atherosclerosis with stenosis or diffuse calcifications, which can make vascular anastomosis of the kidney graft impossible, heterotopic kidney transplant is contraindicated.

There are two alternatives in such cases. First, a kidney transplant in an orthotopic position (with anastomosis of kidney artery to splenic artery, graft kidney vein with its own kidney vein and pyelo-pyelic anastomosis). This is a complex technique, and few centres use it because it requires simultaneous nephrectomy of own kidney and involves greater post-KT complication risks. The second is an aortoiliac bypass before performing kidney graft artery anastomosis to the vascular prosthesis.

Pulmonary disease

Chronic obstructive pulmonary disease (COPD) or severe asthma might be contraindications for KT. There should be a complete assessment (spirometry, oxygen saturation, pulmonary volumes) in cases of moderate disease and maximum optimization of bronchodilator treatment.

Obesity

Extreme obesity (BMI >40 kg/m^2) is a contraindication for KT. In cases of extreme obesity, lifestyle changes should be considered, and in some cases bariatric surgery may be appropriate. Obesity is associated with a high risk of medical (diabetes, infections, venous thrombosis) and surgical complications.

1.2 Abdominal disease profile

Kidney disease

Some kidney diseases may recur after transplant. In some cases, the recurrence is histological and of little clinical importance, whereas in others the recurrence may be early and associated with premature loss of the kidney graft. It is important to know the aetiology of chronic kidney failure.

Systemic disease

The risk of recurrence of systemic lupus erythematosus (SLE) in kidney transplant is low, although the disease should be controlled before transplant. The recurrence of systemic vasculitis (SV) is possible, despite immunosuppressive treatment, so in some cases it is advisable to wait at least 12 months after remission of the disease. This aspect should be carefully evaluated.

Focal segmental hyalinosis

The primary or idiopathic form has a high recurrence risk of (50%) with a rapid progression to CKD, particularly among children, or if it recurred prematurely in a previous KT. The risk of graft loss is high. Therapeutic plasma exchange (TPE) is currently recommended before KT (when there is a live donor) or during the initial postoperative period.

Atypical haemolytic-uraemic syndrome

Atypical haemolytic uraemic syndrome (aHUS) may be idiopathic or familial and is due to defective complement regulation. Mutation can be detected in half of all cases (factor H, factor I or cardiomyopathy). Factor H or I mutations have a high recurrence risk (over 80%) and are associated with a high graft loss rate. Today there is a highly effective treatment available, called eculizumab (anti-C5 antibodies).

Primary hyperoxaluria

Kidney transplantation alone (KTA) is contraindicated given the high recurrence rate that produces a rapid onset of lithiasis with a rapid loss of the kidney graft. The treatment of choice is combined liver and kidney transplantation (CLKT) since it corrects the enzymatic deficit of the liver, which causes this illness.

Digestive disease

Transplantation is contraindicated in patients with active gastric or duodenal ulcer until the condition has been cured. In cases of dyspepsia, screen for helicobacter pylori infection before KT. Diverticulitis or gallstones are not contraindication for KT.

Urological disease

A careful pretransplant evaluation of the bladder is necessary and the presence of a micro or neurogenic bladder may require urological surgery before KT e.g., neobladder. Nephrectomy of native kidneys is indicated in cases of polycystic kidney disease with large kidneys (unilateral nephrectomy is performed to provide space for kidney graft), severe vesicoureteral reflux (VUR), coral form kidney stones, frequent pyelonephritis, and the presence of complicated renal cysts or lesions with a high risk of malignancy i.e., tuberous sclerosis complex (TSC).

1.3 Psychiatric alterations and addictions

Drug addiction or alcoholism are absolute contraindications for KT and at least one year of favourable follow-up at a psychiatric unit specialized in addition is normal before considering transplant. Dementia, severe endogenous depression, schizophrenia or uncontrolled bipolar disorders can be contraindications for a transplant since a regular follow-up and therapy might be difficult. Individual assessment in conjunction with a psychiatrist are needed to assess possible indications for KT, case by case.

In addition, a well-defined intake interview to determine the risk of non-adherence can be important. As kidney transplantation is a treatment with a chronic follow-up and a strict regimen of diet and chronic medication, it is necessary to determine the compliance profile of potential recipients. One risk, and the major reason for graft loss, is non-adherent patient behaviour. This is not an absolute contraindication, but it might require treatment and support from health care professionals to achieve the best long-term results after kidney transplantation. Studies have shown that dialysis vintage, doubts about necessity, and degree of concern about the viability of the graft can lead to non-adherence. Depression can be related to intentional non-adherence.

1.4 Infections

An active infection for any reason is an absolute contraindication for a kidney transplant. There are several potential infections worth bearing in mind when considering assessment for inclusion on the kidney transplant waiting list.

1. **HIV**

   Today, HIV infection in itself is not an absolute contraindication for KT. There is clinical experience showing that KT in selected HIV positive patients has results comparable to those of the general population without negative effects due to HIV infection.

   The current criteria are negative viral load, adherence to antiretroviral treatment, a CD4 count over 200, absence of previous AIDS-defining illnesses (progressive multifocal leukoencephalopathy, disseminated cryptococcus, cerebral lymphoma or visceral Kaposi Sarcoma).

2. Tuberculosis

Active tuberculosis is an absolute contraindication for KT and requires complete treatment before inclusion. When screening the waiting list, conduct a chest X-ray and an enzyme-linked immunosorbent spot (ELISPOT) for tuberculosis (previously, a purified protein derivative (PPD) skin test was common).

Chemoprophylaxis with isoniazid for 6 months (5 mg/kg/day, with maximum 300 mg/day) is indicated for positive ELISPOT or radiological lesions suggestive of prior untreated tuberculosis.

3. Cytomegalovirus (CMV)

It is necessary to know the serological status of the potential recipient for CMV. Over 85% of patients on dialysis are CMV-IgG positive. Patients who are CMV-IgG negative that receive a CMV-IgG positive kidney graft are considered high risk for presenting with a CMV illness after KT and should receive antiviral prophylaxis with valganciclovir during the post-KT period.

4. Epstein-Barr virus (EBV)

Infection with EBV is highly prevalent among the general population. Recipients, particularly children, who are EBV negative before transplant and receive an EBV-positive kidney graft should be followed up during the post-KT period with viral load for EBV.

5. Hepatitis B virus (HBV)

An HBV infection is not an absolute contraindication for KT. A complete assessment must be conducted to ascertain the degree of liver involvement (DNA-HBV viral load, ultrasound, FibroScan®, haemodynamic study, esophagogastroduodenoscopy (EGD) and transjugular liver biopsy).

In hepatitis B surface antigen (HBsAg) positive and DNA-HBV positive patients, antiviral treatment (lamivudine, tenofovir, entecavir) must be administered during dialysis prior to kidney transplant, which makes the viral load negative in most cases. In the absence of severe hepatopathy and once DNA-HBV has been negativized, KT is possible, although antiviral treatment must be maintained indefinitely.

In cases of liver cirrhosis, kidney transplant is contraindicated, whereas the CLKT is indicated.

6. Hepatitis C virus (HCV)

Although HCV infection is not an absolute contraindication, kidney transplant will depend on the degree of liver disease.

Nevertheless, a kidney transplant in patients with HCV is associated with lower patient and graft survival, and a higher risk of presenting with infections. A complete liver assessment (RNA-HCV viral load, genotype, alpha-fetoprotein (AFP), ultrasound, FibroScan®, haemodynamic study, EGD and transjugular liver biopsy) is required.

Traditionally, patients with HCV were given antiviral treatment with interferon and ribavirin before a kidney transplant (as this treatment is contraindicated during the transplant due to risk of inducing acute rejection).

Currently, there are new antiviral treatments (sofosbuvir, simeprevir, boceprevir, etc.) that have great therapeutic efficacy since they are curative in a large proportion of cases. In the absence of severe hepatopathy, KT is possible. Should the virus not be negativized, new antiviral drugs must be assessed. As with HBV, in cases of liver cirrhosis, a CLKT should be considered.

1.5 Neoplasia

Immunosuppressive treatment may accelerate tumoral growth, so screening for hidden neoplasia is required as is a detailed assessment of any previous neoplasia.

Active or a recent neoplasia is an absolute contraindication for KT. Patients who had a previous neoplasia should undergo a waiting period before transplantation to check their evolution and avoid post-KT recurrence.

This waiting period is variable and will depend on tumour type and stage.

There are 3 types of waiting period:

- **No wait:** Carcinoma *in situ*, incidental kidney carcinoma under 2 cm, low-grade bladder neoplasia and non-melanoma skin carcinoma.
- **2-5 year waiting period:** Prostate, bladder, or testicle neoplasia, lymphoma, leukaemia, thyroid neoplasia, melanoma *in situ*.
- **Waiting period exceeding 5 years:** Breast, colon, lung, womb, and kidney carcinoma (over 5 cm or invasive).
- **Absolute contraindication:** Multiple myeloma (consider prior bone marrow transplant), uncontrolled malignant tumour.

2. RECIPIENT WORKUP AND ASSESMENT

During the recipient workup it is important to eliminate, as far as possible, any unforeseen clinical aspects that may jeopardize or influence a good outcome at the time of transplantation. It is also important to note details of the recipient's immunological profile.

A standardized and thoroughly managed kidney transplant workup directly influences the clinical outcomes of the kidney transplantation.

2.1 Medical history

It is essential to compile a detailed clinical history and conduct a complete physical examination. The anamnesis must include a complete nephrological history (reason for kidney failure, dialysis modality, duration, complications, vascular accesses, prior kidney transplants and treatments administered). In addition to the classical work-up, the medical history should pay particular attention to:

- **Cardiovascular assessment** (exclude major cardiovascular risks related to direct perioperative and postoperative complications as well as possible graft failure).
- **Immunological profile of the patient:** this is important in order to avoid or monitor the risks of acute rejection.

2.2 Cardiovascular assessment

1. First level cardiological assessment

This is the basic cardiological workup that all prospective KT waiting list candidates should undergo. It consists of evaluating:

Cardiovascular risk factors (HBP, dyslipidaemia, diabetes, obesity, smoking, a family history of premature vascular disease), prior history of cardiovascular disease (heart failure, ischaemic heart disease, cerebrovascular disease, and peripheral vasculopathy), ECG, chest X-ray and echocardiogram.

2. Second level cardiological assessment

A cardiac stress test or stress echocardiography consisting of an ultrasound of the supra-aortic trunks (to assess carotid stenosis) and an exercise stress test, which can be of two kinds: isotopic (myocardial SPECT scan with or without dipyridamole-thallium) or a stress echocardiogram with dobutamine. This is indicated for patients with diabetes, over the age of 60, with a prior or current history of ischaemic heart disease, ECG alterations suggesting ischaemia or echocardiogram alterations (significant valvular heart disease or cardiomyopathy).

3. Third level cardiological assessment

This is performed in the event of negative results in either of the two previous assessments. If the results of the exercise stress test are positive for ischaemia, the patient must be examined by a cardiologist to evaluate the need for cardiac catheterization.

Should a significant coronary atherosclerosis be discovered, a coronary revascularization procedure will be considered (angioplasty with or without stent or aorto-coronary bypass). The use of stents, particularly drug-eluting stents, requires drug antiplatelet therapy (DAPT) (ASA and clopidogrel) for a period of 6 to 12 months, which forces inclusion on a KT waiting list to be delayed.

2.3 Urological assessment

1. Basic study

Current indications are for an abdominal CT with vascular reconstruction (angio-CT) in all patients. For young patients it is possible that only a complete abdominal ultrasound may be required. Kidney size should be evaluated, and the presence of complicated cysts or ganglions ruled out. An angio-CT enables detailed assessment of vascular aortoiliac calcifications, the existence of vascular stenosis, and bilateral circulations, in addition to simultaneously informing on the splenic artery status in the case of orthotopic transplant.

2. Prostatic study

Men over the age of 50 should undergo a prostate-specific antigen (PSA) test and a rectal examination. Flowmetry is of little value since the patient is on dialysis.

3. Voiding cystourethrography

The indications for this test are currently restricted. Although it is indicated in some cases with a history of vesicoureteral reflux, repeat urinary infections, genitourinary tuberculosis, prostatic hypertrophy, urological interventions or prolonged haemodialysis.

4. Urodynamic testing

If a neurogenic bladder is suspected, patients should undergo testing for bladder functional impairment, in some cases this should include a cystometry.

5. Other studies

Depending on the urological history, other studies may be necessary such as urinary cytology, cystoscopy or a Uro-CT.

2.4 Immunological assessment

Blood group, HLA typing, anti-HLA antibodies (CDC, Luminex class I and II) must be determined. In the event of results indicating positive for anti-HLA antibodies, single antigen testing must be conducted to determine complete specificity (Figure 2).

Waiting time, the possibility of matching and the impact on a positive long-term outcome are determined by the potential recipient's immunological profile (Figure 3). Based on this assessment, patients can be properly informed on how the months on the waiting list will proceed.

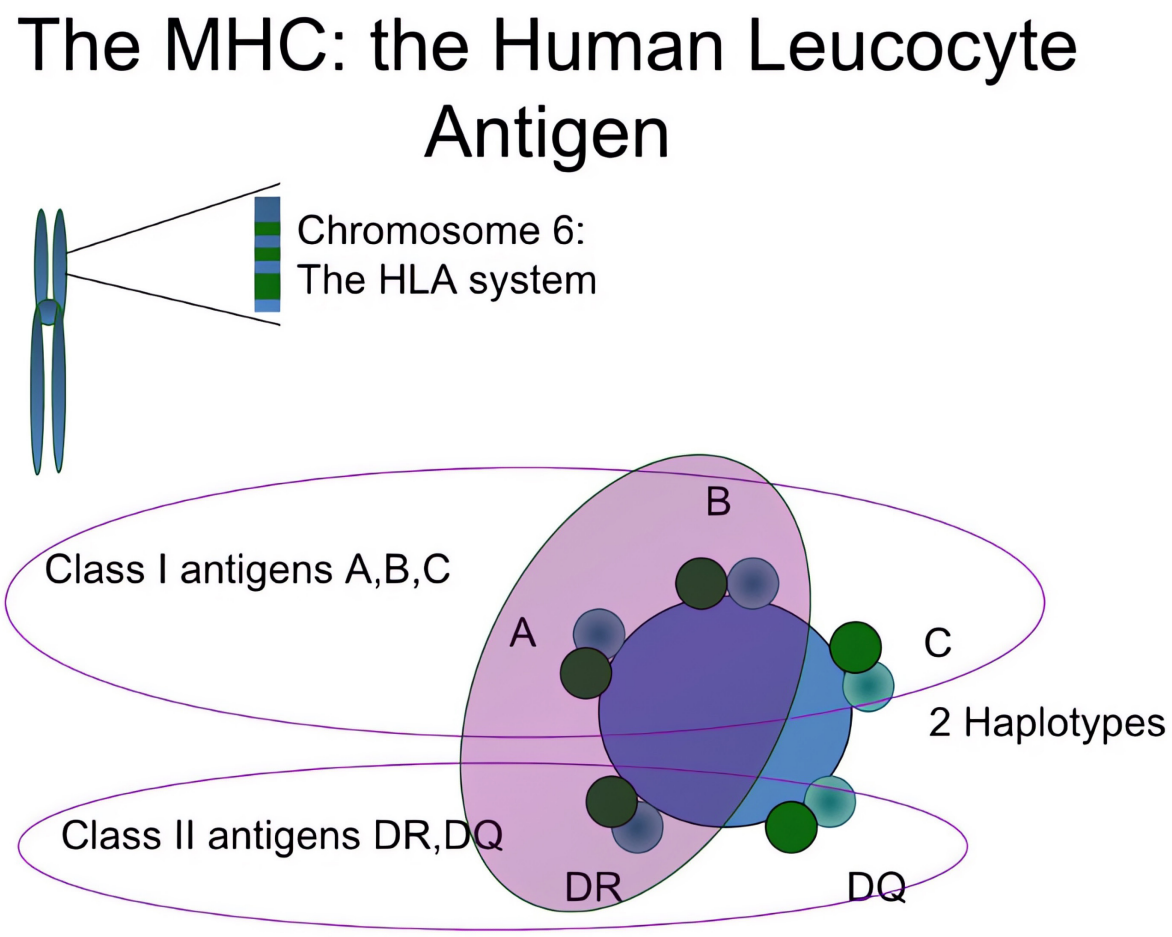

Figure 2. The immune risk profile of transplantation.

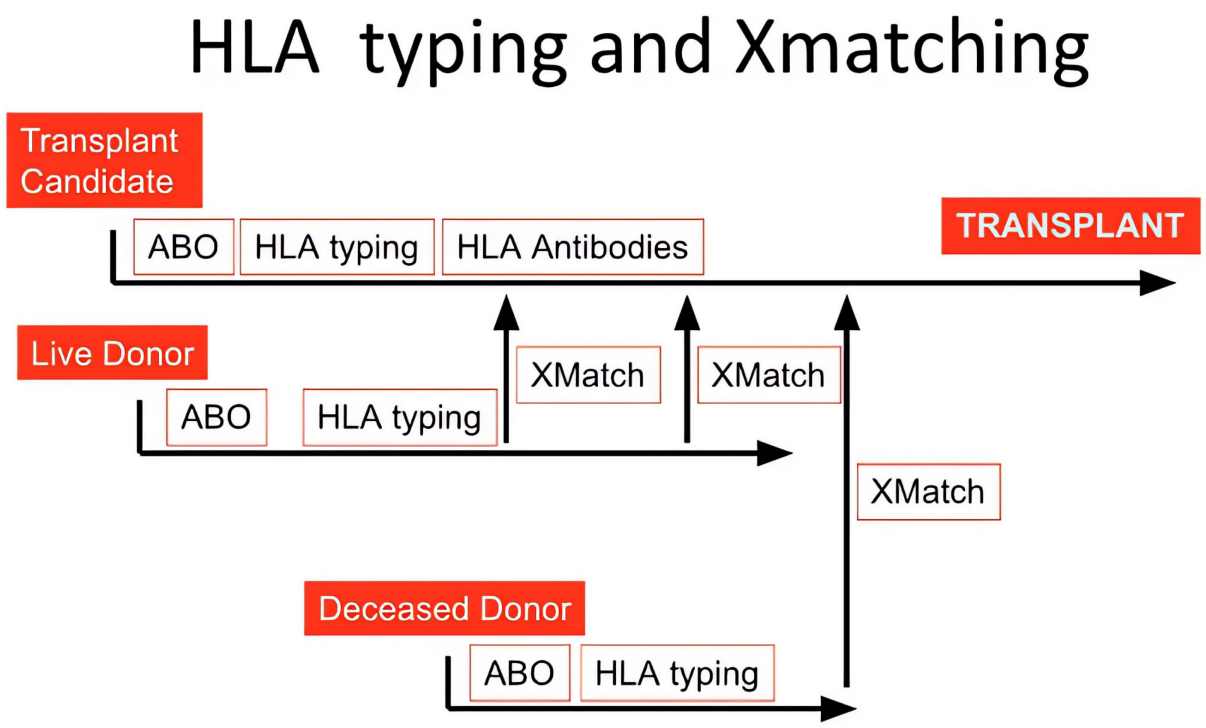

Figure 3. The immune risk profile of transplantation 2.

2.5 Infection assessments

Immunization

The patient's vaccination calendar should be reviewed and updated in accordance with current indications and level of previous immunization according to serological results. Vaccination is recommended against hepatitis A and B, pneumococcus, meningococcus, haemophilus, tetanus, diphtheria, and varicella-zoster virus (VZV). Evaluate and consider vaccination against papilloma virus for young women.

Hepatitis B + C Virus (HBV + HCV)

HBV

In the event of a patient being HBsAg positive, viral load must be determined (DNA-HBV). Once chronic HBV has been confirmed, complete liver assessment is required, i.e., abdominal ultrasound, FibroScan® and AFP. If chronic liver disease is suspected (increased liver echogenicity or FibroScan® > F2), the study must be completed with a hepatic haemodynamic study (to assess portal hypertension and rule out varicose veins), plasma AFP and transjugular hepatic biopsy (to assess the degree of liver involvement).

HCV

On detecting IgG-HCV (ELISA) viral load, RNA-HCV must be determined. As with chronic HBV, a full evaluation of the liver is necessary, i.e., abdominal ultrasound, FibroScan® and AFP, and virus genotype. If chronic liver disease is suspected, it is necessary to perform a hepatic haemodynamic study, EGD and transjugular hepatic biopsy (to assess the degree of liver involvement).

Table 3 shows complete assessment of kidney transplant recipients. On the day of the transplant, the tests to perform are an immunological study (crossmatch), an analytical study (basic biochemical profile, haemogram, clotting, blood reservation and serologies), complementary tests (chest and abdomen X-ray, ECG) and informed consents (for transplant, transfusion, and kidney biopsy).

Table 3. Kidney transplant recipient study

MEDICAL HISTORY
Detailed anamnesis: current clinical conditions, toxic habits, allergies, previous history of neoplasia, infections, illnesses, and surgeries
Nephrological history: reason for kidney failure, dialysis type (duration, complications), vascular accesses (internal AV, vascular prosthesis), previous transplants (cadaver/living, re-transplant, treatment administered)
Physical examination: weight, height, BMI
IMMUNOLOGICAL STUDY
Blood group, HLA typing, anti-HLA antibodies (CDC, Luminex), single antigen (if PRA positive)
MICROBIOLOGICAL STUDY
Viral serology (HBsAg, HCV-lgG, HIV, CMV-lgG, HTLV-I, HSV-lgG, EBV-lgG), toxoplasmosis-lgG, syphilis
ANALYSES
Biochemistry, proteinogram, haemogram, lipid profile
Hormone study (PTH, vit D, TSH, T3)
Clotting
Faecal occult blood test (over age 50)
Thrombophilia study (if a history of thrombosis)
Tumoral markers in special groups (PSA, AFP, CEA...)
CARDIOVASCULAR STUDY
Chest X-ray
ECG
Echocardiogram (HBP, over age 40 or ECG abnormalities)
SPECT-dipyridamole exercise stress test (over age 50-60, diabetes, ECG abnormalities suggesting ischaemia, history of coronary illness, multiple cardiovascular risk factors)
Coronary angiography (positive exercise stress test or history of angina or previous heart attack).
Carotid ultrasound (diabetes, cerebrovascular disease, carotid murmurs, over age 65)

UROLOGICAL STUDY

Abdomen and vesicoprostatic ultrasound (men)

CT and Angio CT (over age 40, re-transplant, diabetes, cardiovascular disease)

Cystography (urological disease, over 5 years on dialysis, over age 60)

Urodynamics (neurogenic bladder)

PSA (men over age 50)

GYNAECOLOGICAL STUDY

Mammography (women over age 40)

Smear test and gynaecological assessment

Others in accordance with findings (transvaginal ultrasound, hysteroscopy)

DIGESTIVE STUDY

Colonoscopy (over age 50 or with a history of polyps and familial rectal carcinoma)

EGD (clinical ulcer)

OTHER STUDIES (In accordance with findings and history)

Respiratory pathology: breathing tests, bronchoscopy

Neurological pathology: CT or CRN, EEG, EMG

TRANSPLANT TEAM ASSESSMENT

Nephrology, urology, anaesthesia

Ethics committee

Civil registry (living donor)

3. TRANSPLANTATION RECIPIENT SELECTION

Recipient selection for a kidney transplantation is a complex process that aims to find the best recipient for a kidney donor. The importance of the different criteria may vary between centres. Currently, the duration of dialysis and immunological compatibility have great importance. The following are an example of the criteria followed in a major Spanish centre.

Level 1: According to blood group (isogroup) compatibility criterion. The following priorities are established:

1. Medical emergency (absence of vascular accesses or impossibility of peritoneal dialysis).
2. Immunological emergency (hyper-sensitized patients with negative virtual crossmatch).
3. Combined transplant (liver-kidney, pancreas-kidney, or heart-kidney).
4. Other priorities (primary dysfunction of previous kidney transplant, desensitization treatment).
5. HCV-positive donor (a positive RNA-HCV recipient is selected) or HBsAg-positive donor (a positive HBsAg recipient is selected).

Level 2: Three criteria are established:

1. Donor/recipient age (donors under 40 are implanted in recipients under 40; recipients within an age range of +10/-10 years are sought for donors over 40.
2. Time on waiting list (priority given to recipient with longest time on list).
3. Immunological compatibility and absence of specific donor antibodies (recipient with greatest HLA identity has priority).

Level 3: Once selected, CDC crossmatch must be conducted between the recipient and donor serum:

Lymphocytes. This test must be negative. A cytometry crossmatch may also be conducted in case of a living donor transplantation (if positive, desensitization treatment must be administered before transplant).

(Table 4) summarizes the selection criteria of a kidney transplant recipient.

Table 4. Selection criteria of a kidney transplant recipient

Level 1: (group identity)
Paediatric urgency
Medical urgency (complete lack of dialysis accesses)
Immunological urgency (hypersensitized patient with negative virtual crossmatch)
Combined transplant (liver-kidney, pancreas-kidney, heart-kidney)
Primary dysfunction of a previous transplant
HCV positive donors (implanted in RNA-HCV positive recipients)
HBsAg positive donors (implanted in HBsAg positive recipients)
Level 2:
Donor age (D <40 to recipients <40; D >40 to recipients +/- 10 years)
Time on waiting list
HLA compatibility
Absence of donor-specific alloantibodies (DSA)
Level 3:
CDC crossmatch: if positive, KT is contraindicated
Cytometry Crossmatch (only possible in live donor): If positive desensitization therapy should be considered pre-KT

CONCLUSIONS

» A kidney transplantation is indicated in patients with CKF stage 5 in dialysis or pre-dialysis, with an absence of contraindications, who wish to be transplanted. Absolute contraindications are a positive crossmatch, advanced age (elderly), active neoplasia, uncontrolled infection, generalized atherosclerosis, serious psychiatric illness, drug/alcohol addiction or serious organic disease that reduces the patient's life expectancy (cardiopathy, COPD, liver cirrhosis, neurological disease). Nevertheless, there are a large number of intermediate clinical situations that require individual, case by case consideration.

» Recipient assessment is essential for correct KT indication. It is obligatory to perform a full immunological study (blood group, HLA typing, anti-HLA antibody search), microbiological study, cardiovascular assessment and urological study. Cardiovascular assessment is highly important, particularly in patients over the age of 60, diabetics or who have undergone prolonged dialysis. In these cases, an isotopic exercise stress test is required to detect a subclinical coronary disease which, if positive, will require a coronary angiography. The basic urological evaluation examination is a CT/angio-CT and any other studies are conducted on an individual basis according to the patient's individual risk.

» Finally, recipient selection for a kidney donor is a complex process whose objective is to find the best recipient. The criteria used in our centre are based on three levels. First, the order of priority is paediatric transplants, medical emergency, immunological emergency and combined transplants. Secondly, after completing age matching, the patient with most time on dialysis with the appropriate immunological compatibility and absence of DSA antibodies is selected. Finally, a CDC crossmatch between donor and recipient must be conducted and, if negative, the kidney transplant can go ahead.

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TOPIC 2 - Unit 2

Organ evaluation and surgical procedure (techniques and surgical complications)

ORGAN TRANSPLANTATION

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INTRODUCTION

Kidney transplantation requires the combination of a medical and a surgical approach, which are both equally important. It is well documented that the failure of either of these two approaches results in worse functional outcomes for the transplantation.

This means it is essential to be aware of every detail that can influence the procedure and cause complications or negative outcomes. In terms of surgery, there are three main areas to consider: organ evaluation, kidney transplantation techniques and surgical complications, which may appear in the postoperative period.

This unit deals with these three areas of interest, devoting one section to each. Section 1 provides a description of the evaluation criteria a surgeon must take into account when deciding the viability of a graft, highlighting the importance of macroscopic evaluation and additional tools like biopsy and pulsatile perfusion parameters.

Section 2 discusses the different techniques for kidney transplantation (heterotopic and orthotopic) and describes the key points for a good surgical technique. Finally, section 3 considers the different surgical complications we must prevent and explains and how to deal with them.

1. ORGAN EVALUATION

Within the kidney transplantation process, evaluation of graft viability is essential. Unquestionably, initial dysfunction of the graft not only has a serious negative impact on functionality, but also a major economic impact. Furthermore, there is a small percentage of grafts which will either never become functional or will function poorly in the medium and long term. We use different tools to assist in the decision to accept a graft.

- Regarding the evaluation of organ viability, we consider:
- information about the donor;
- information about the extraction process;
- macroscopic aspects of the kidney;
- histological assessment;
- hypothermic pulsatile perfusion (resistance index);
- molecular markers and biomarkers.

This section will deal with macroscopic aspects of the kidney, histological acceptance criteria and machine perfusion.

1.1 Macroscopic evaluation

Macroscopic evaluation of the kidney provides information on perfusion, the presence of lesions, malformations, anatomical variations, and other characteristics of the kidney. It is the responsibility of the extracting surgeon, who always has information about the donor and preservation of the organ, to decide on the organ's suitability. There are no studies which evaluate the validity and predictive value of this tool, despite the system being worldwide [1].

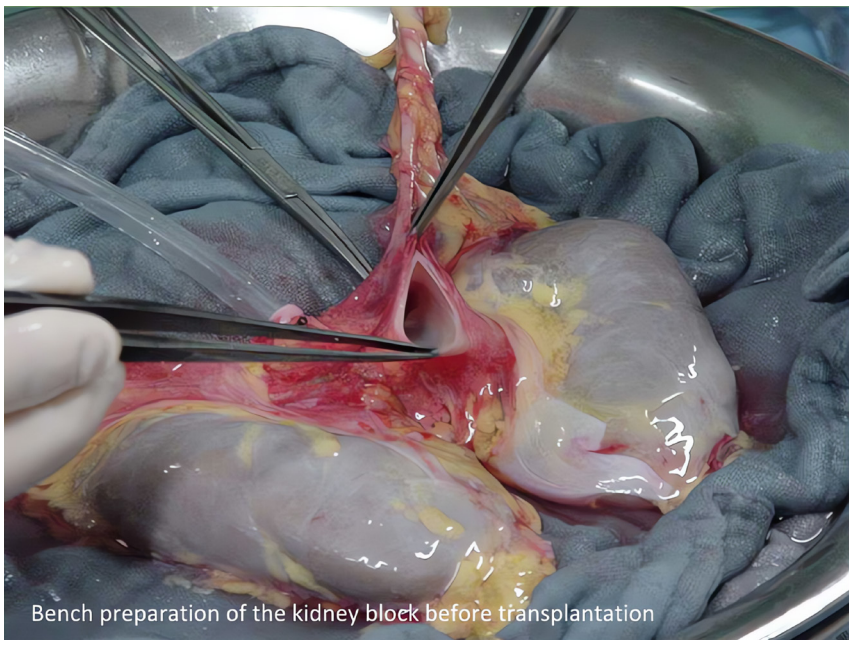

Figure 1. Bench preparation of the kidney block before transplantation.

1.2 Biopsy

Histological evaluation with a graft biopsy prior to transplantation is usually done selectively, particularly on kidneys with a reduced viability risk or from heart attack donors. However, the use and weight of biopsies in acceptance is highly variable and depends on the policies of each centre.

A histological study values the percentage of glomerulosclerosis, vascular lesion and interstitial fibrosis. These three factors have been demonstrated to have an association with the worst graft evolution. Despite this, there is currently no consensus regarding the relative importance of each factor, or the relation they have with the donor and recipient's risk factors.

Different scores such as the Remuzzi score, Banff criteria, Maryland Aggregate Pathology Index (MAPI) have been developed for histological evaluation, although there is no consensus regarding their use [2-4].

1.3 Hypothermic pulsatile perfusion

The use of hypothermic and normothermic machine perfusion has seen renewed interest in the last decade, as it enables better graft preservation in addition to providing information on graft vascularization. Studies have documented how the vascular resistance index is a predictive factor for graft function delay, and even primary failure, despite no cut-off point having been established [5-7].

Despite this evidence, the low prediction power of this index means that use of vascular resistance is not recommended as the sole tool for evaluating graft viability because kidneys with high resistances may present acceptable results [8].

Furthermore, machine perfusion enables perfusion liquid samples to be taken and analysed for evaluation of the presence of tissue lesion biomarkers and viability prognosis. However, there is currently no validated marker for use in clinical practice [1].

Figure 2. Hypothermic pulsatile machine perfusion.

1.4 Donor scores

In order to compile clinical information about donors, different score systems have been developed to predict the onset of graft function delay and graft viability [9-12].

Some of these systems include histopathological information combined with clinical risk factors [13]. However, no consensus exists about whether they should be used as the sole criterion to decide graft viability.

2. SURGICAL TECHNIQUE

The surgical technique for classical kidney transplantation (heterotopic kidney transplantation) is an almost universally standardized procedure in all centres.

Classic open kidney transplantation is considered a minor abdominal procedure due to its retroperitoneal approach. Nonetheless, this procedure can currently also be performed using minimally invasive surgery, such as robotic surgery, in experienced centres.

Complications depend on the comorbidity factors of both donor and recipient. This is particularly the case with vascular complications, in which obesity and diabetes are aspects to take into account during the kidney transplantation procedure.

2.1 Heterotopic kidney transplant

A conventional kidney transplant is one in which the kidney is implanted with heterotopic placement, either in the right or left iliac fossa via an extra-(retro) peritoneal approach, performing anastomosis of the graft vessels to the iliac vein and artery in end-lateral position. The anastomosis site has varied over time; however, the important matter is to obtain a correct placement of the kidney vessels so there are no bends or tension points that hinder correct graft perfusion and drainage. Placement of grafts in distal position (outer iliac vessels) facilitates vascular dissection of the recipient and distinguishing ureter length, thereby avoiding urinary tract complications.

The patient can be laid on their back or side, tilting the operating table slightly so as to achieve a better exposure field. After asepsis and adjustment, we make an external para-rectal extra-peritoneal incision. This incision, which may be J-shaped, should reach the side corner of the pubis so the ureter can easily be reimplanted. After dissection, the epigastric vessel is ligated and, in the case of women, a round ligature relocating the peritoneum to a cephalo-medial position facilitates exposure of the desired surgical field.

We place the kidney in the best position for both anastomoses. Next, we dissect the iliac vessels, limiting ourselves to the area of the anastomosis. It is important to perform the least dissection possible and ligate the lymphatic vessels to prevent secondary lymphocele.

Keep the kidney at a low temperature during anastomosis (cold ischaemia). If it is possible, recommendations are to place one cold compress (crushed ice wrapped in gauze) below the kidney and another on top.

Venous anastomosis

Firstly, a Satinsky clamp is placed at the outer iliac vein level and a small venotomy is performed. We instil diluted heparin 0.04% via a Medicut to wash the blood remains. Next, we enlarge the venous opening with scissors (the size must be adjusted to the size of the renal vein in the graft). On occasion, one of the vein walls may need slight cutting back to facilitate anastomosis. There are two ways of performing the anastomosis: with or without moving the kidney. This anastomosis can be performed with Prolene 5/0 or 6/0 suture. To perform an anastomosis without moving the kidney, the suture is placed on one vertex and knotted. The same manoeuvre is repeated on the other end. The posterior suture starts on the internal face of the vein, allowing us to suture comfortably without having to mobilize the kidney. On completion of the posterior face, we knot the suture. The same action is performed for a second time on the anterior face of the vein (Figure 3). On completion of anastomosis, blood leakage (tightness) prior reperfusion can be verified by fitting a bulldog clamp on the proximal part of the kidney vein.

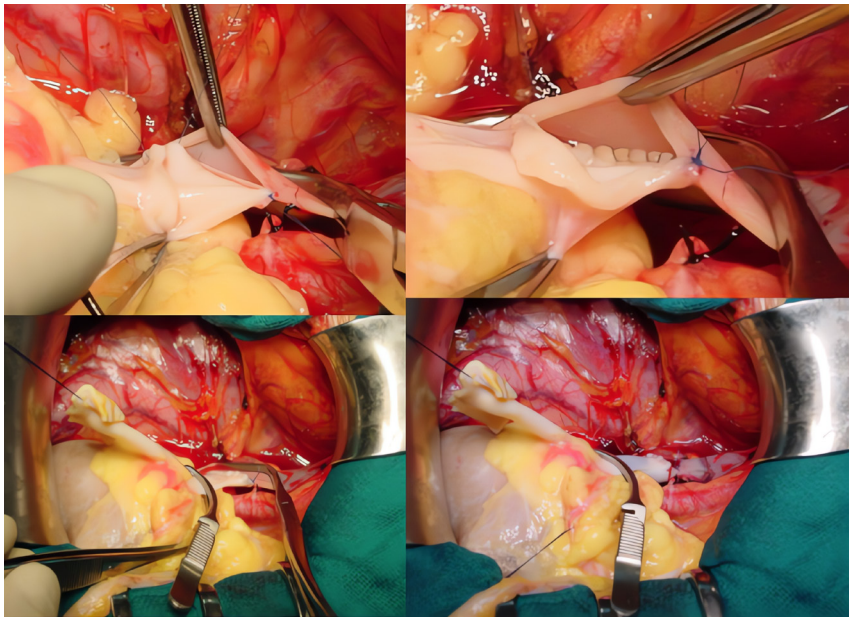

Figure 3. End-lateral venous anastomosis to outer iliac vein.

Arterial anastomosis

On vein completion, arterial anastomosis begins. This is performed using a single suture of Prolene 6/0 or 7/0 in accordance with renal artery size and patch existence. As with the vein, we suture the posterior wall to the inner face to complete it via the anterior face. Again, check its tightness and unclamp (Figure 4).

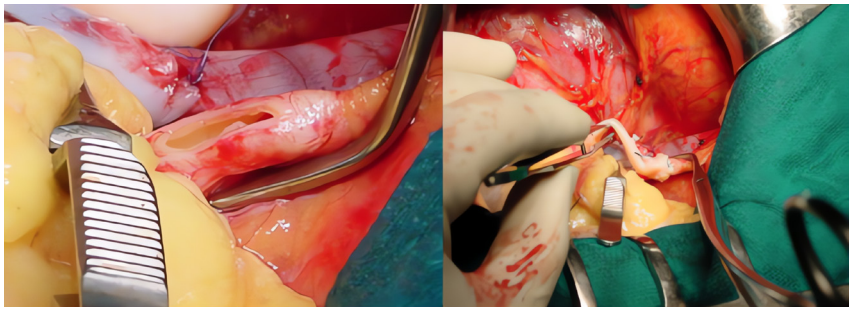

Figure 4. Arterial suture.

Urinary tract anastomosis

There are several surgical techniques for urinary tract anastomosis, such as anastomosis of ureter to bladder, which may be extra- or intravesical; or anastomosis of tract to the ureter itself, among others.

One intravesical technique is the Politano-Leadbetter, which consists of a transversal incision from vesical cupule level to its aperture. Secure to the wall with a triangular fixation and make a field using a malleable valve. We make a submucosa tunnel to introduce the ureter, flatten the end of the ureter and fix it with three sutures of resorbable stitches 6/0. The hiatus should be closed with the same suture. Finally, we close the bladder with two continuous sutures of resorbable gut (Figure 5).

Transposition of the iliac vein is a manoeuvre that enables reduction of the distance of venous anastomosis in cases where the vein is short or where the arterial anastomosis overlaps. Greater dissection of the vessels is necessary to perform this manoeuvre to allow them greater mobilization. This is routinely used in some centres in right living donor cases where the layout of anastomoses overlaps. This technique offers results comparable to a conventional transplant [14].

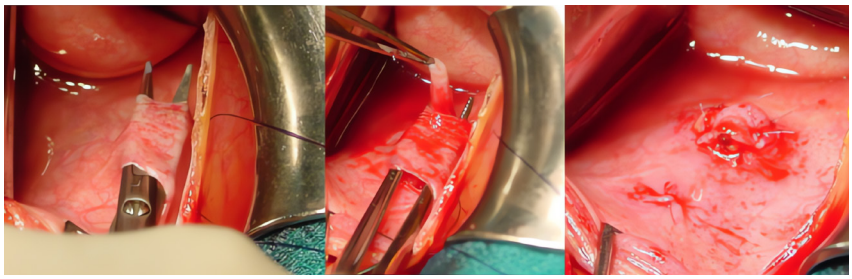

Figure 5. Ureteral reimplantation (Politano-Leadbetter).

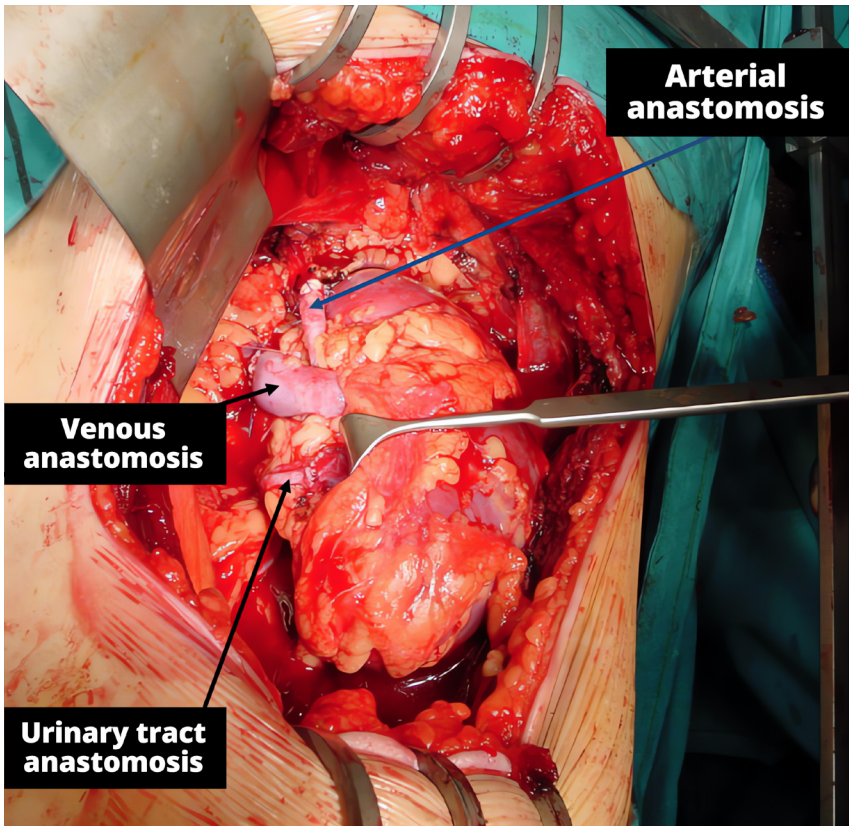

Figure 6. Final result of orthotonic transplant.

2.2 Orthotopic transplant

The orthotopic kidney transplant technique arose from Professor Gil Vernet's 1978 description of a new extraperitoneal approach of the splenic vessels, and it was developed to treat kidney hypertension secondary to kidney artery stenosis [15]. The results of the largest orthotopic transplant series, with a total 139 cases, were published in 1989 [16].

The majority of the recipients in the series were young and without vascular pathology. The orthotopic transplant was indicated to avoid use of the internal iliac artery (the technique used at the time) and its consequences, which included associated erectile dysfunction. This technique has become imperative since 1987 and is reserved for patients for whom heterotopic kidney transplant is impossible (severe atheromatosis, lower vena cava thrombosis, iliac fossae occupied by previous transplants) [17].

This is a complex surgical technique involving an open nephrectomy (lumbotomy), with preservation of the kidney vein and urinary tract, in addition to dissection of the splenic artery to subsequently perform the implant.

Surgical technique

The patient is placed on their right side in order to perform a large lumbotomy with resection of the twelfth rib. Nephrectomy is performed via retroperitoneum and should be done very carefully, avoiding excessive movement and dissection of the urinary tract. The kidney artery may be directly ligated, since these are small arteries in the majority of cases, so they cannot be used for kidney revascularization.

Next dissect the kidney vein to the hilum, ligating each of the small branches separately. This enables maximum enlargement of the kidney vein diameter. Finally, dissect the urinary tract to intra-parenchymatous level, preserving the kidney calyces.

On completion of the nephrectomy, locate and dissect the splenic artery. This is located behind the adrenal gland. In thin patients, this can be seen transparently and by palpation. Dissection of the splenic artery should reach its bifurcation, and care should be taken to avoid splenic vein spasm and bleeding. Once dissected, we ligate the distal end and place a bulldog clamp on the proximal end, checking good arterial flow exists. The kidney vein previously ligated along all its small branches is prepared so we obtain the largest diameter possible leaving it clamped with a bulldog. As with the heterotopic kidney transplant, we place a cold compress on the surgical table to maintain the kidney at a low temperature throughout surgery.

First, venous anastomosis is performed via two continuous sutures of Prolene 6/0, subsequently checking their tightness. Secondly, end-end arterial anastomosis is performed between splenic and graft renal arteries with two continuous sutures of Prolene 6/0 or stitches. Finally, urinary tract anastomosis is performed, which may be pyelo-pyelic, pyelo-ureteral or ureter-ureteral. As already mentioned, dissection of the urinary tract itself should be minimal and avoid tension to preserve its vascularization to the maximum. Anastomosis is performed via two continuous sutures of Monocryl 6/0. The urinary tract is left tutorized by a double-J pigtail and minimal Gil Vernet nephrostomy. The image shows the final result of the orthotopic kidney transplant (Figure 4).

3. SURGICAL COMPLICATIONS

The complications arising after kidney transplant have reduced over the years thanks to multiple factors, among which are a reduction in corticosteroid doses and the development of surgical technique.

Despite this, kidney transplantation is an important source of morbidity and mortality, and its complications may compromise both viability of the graft and recipient survival. This section will describe the most common complications and their most appropriate treatment [18].

3.1. Urological complications

Urological complications are those related to the native or transplanted urinary tract. Although, 30 years ago they appeared in 10-25% of transplants, their current incidence is 2.9-9.2%. Urinary fistulas and ureteral stenosis are the most frequent, representing 95% of all urological complications.

Urinary fistulas

In most cases, they appear due to technical failures, which will cause vascular failure, ureter ischaemia and necrosis. Their incidence is between 0.8 and 23%, although the use of double-J pigtail catheters helps reduce onset, for which reason many teams use them systematically.

The fistula can develop at any point on the urinary tract but are most frequent at anastomosis level (ureter-vesical, ureter-ureteral, ureter-pyelic).

They appear prematurely with urine leakage through the drainage tube, or swelling in the transplant area and anuria if drainage has been removed. Less frequently, oedema of lower ipsilateral limb may appear due to compression.

Diagnosis is via analysis of the liquid obtained, whether from the drainage tube or via fine needle aspiration. A Differential diagnosis should be considered with a lymphocele, so creatinine levels from the liquid obtained must be determined (which are higher than creatinine levels in plasma in the event of fistula).

To determine the location and size of the fistula we can use gammagraphy, cystography, urography and retrograde or anterograde pyelography with nephrostomy.

Treatment depends on the location and severity of the fistula. Immediate surgery may be considered or delayed via nephrostomy. Undoubtedly, this technique has enabled an improvement in prognosis for patients with ureteral fistulas.

Ureteral stenosis

Some groups describe this as the most common complication, which appears in up to 5.5% of transplants. The vast majority (80%) are located in the uretero-vesical anastomosis.

We should differentiate between premature and delayed stenosis. The former is due to oedema, compression due to bruising or technical errors (ureteral torsion, transfixion points, etc.). Stenosis presents with an alteration of kidney function and ureter-hydronephrosis, confirmed via anterograde pyelography. The insertion of drainage (percutaneous nephrostomy or double-J pigtail catheter) may be sufficient as temporary treatment until disappearance of the cause. A new ureter-vesical anastomosis is indicated if the situation does not resolve.

Delayed stenosis (several weeks after transplant) is due to vascular defects after extraction, although they are not sufficiently serious to cause necrosis of the ureteral wall and subsequent fistula. Delayed stenosis is also related to rejection and the type of uretero-vesical anastomosis performed.

The clinical presentation is altered kidney function, which may be accompanied by a reduced volume of diuresis and is sometimes associated with fever and abdominal pain.

The first diagnostic test is an ultrasound, which will show dilation of the urinary tract. A gammagraphy will show good contrast capture, serving to rule out possible rejection (capture reduction or absence and elimination). Finally, endovenous urography or anterograde pyelography via a nephrostomy catheter will establish delimitation of the level of stenosis.

Regarding treatment, catheter balloon dilation (anterograde or retrograde) may be used in short stenosis, associated or not with an endo-ureterotomy and the subsequent placement of a double-J pigtail catheter. Results are variable, although some groups report success rates of 100% in selected groups.

Vesical-ureteral reflux

Depending on the type of anastomosis used, the incidence of reflux ranges between 0.6 and 50%. Best results are obtained with intravesical antireflux techniques (e.g., Politano-Leadbetter).

The mechanism whereby reflux damages the graft are repetitive urinary infections or vesical hyperpressure. In the absence of these, the negative impact of reflux has not been clearly established.

Ureter-vesical anastomoses using the antireflux technique are the best method to prevent lesions due to reflux, even though they involve an increase in the number of ureter-vesical union stenosis.

Lithiasis

The incidence of lithiasis in grafts is under 2%, and onset is due to persistent hyperparathyroidism, recurrent urinary tract infection (UTI), presence of foreign bodies, tract ectasia, reduction of fluid intake and distal renal tubular acidosis.

The main characteristic of lithiasis in a transplanted kidney is non-presentation of renal colic symptoms as the organ is non-innervated. Therefore, lithiasis should be suspected when there is a brusque worsening of kidney function or graft kidney infection.

Lithotripsy is not contraindicated for a transplanted kidney, thus treatment is identical to native kidney lithiasis, i.e., identification of a stone by means of imaging tests and then application of the most appropriate treatment in accordance with the characteristics and location of lithiasis. It should be highlighted that a uretero-renoscopy is more difficult because it is a neomeatus.

Haematuria

Haematuria after kidney transplant is a surgical complication due to a lesion somewhere in the urinary tract. If the origin is renal, onset is usually due to the insertion of a nephrostomy catheter or after a renal biopsy. Should the degree of haematuria allow, expectant management will be sufficient. In the case of serious haematuria where vesical origin has been ruled out, an arteriogram is indicated to attempt selective embolization of the vessel causing the haemorrhage.

Haematuria of vesical or ureteral origin begin in the ureteral tip or cystotomy. Try to control haematuria with continuous bladder washing. Persistence of haematuria will require endoscopic revisions to clot the bleeding spot.

Delayed onset haematuria (several weeks after transplant) will require a complete study of the patient with imaging tests, cystoscopy, etc. This is because it may not be directly related to the transplant but the result of a tumoral process, lithiasis, infection, etc.

Urinary infection

The onset of urine infections in transplant patients is frequently due to several factors such as the use of immunosuppression, a vesical catheter, urinary tract manipulations, or association with an illnesses like diabetes, etc.

During the first three months posttransplant, wide spectrum antibiotic treatment is generally administered as prophylaxis.

Urinary infections appearing months after transplant generally respond quickly to antibiotic treatment. The presence of obstruction or lithiasis should be ruled out in patients presenting with kidney infection. In the event of obstruction, urinary tract drainage with administration of endovenous antibiotics therapy is indicated.

3.2. Vascular complications

In the early days of transplant surgery, vascular complications had an incidence of up to 30%; however, this figure is currently between 1.9 and 8%. These complications are related to technical aspects of surgery, prior atheromatous lesions, the appearance of thrombosis, lymphocele, etc., and may affect graft and recipient vessels.

Although it has not been demonstrated that the presence of multiple kidney arteries is the cause of the onset of vascular complications or that it worsens graft or recipient survival, grafts with multiple arteries are associated with a higher number of haemorrhagic complications.

Kidney artery stenosis

This represents 75% of vascular complications after transplant. Its incidence is around 3%, depends on the type of anastomosis, and it is more frequent with end-end sutures. The main reason for technical failure is related to performing anastomosis. Other factors are pedicle elongation, excessive dissection of adventitia, vasospasm due to excessive manipulation, the interposition of adventitia in anastomosis, arterial intussusception, bending, torsion or lesion of the intima during perfusion.

The clinical onset of arterial stenosis is non-specific and is characterized by HBP related to the medical treatment and/or absence or worsening of graft function.

The initial examination is of kidney vessels via Doppler ultrasound. We will detect an increase in blood flow velocity at the point of stenosis with deceleration of the distal area immediately secondary to the increase of the vascular beam. An angio-MR study can be performed, which provides greater sensitivity and specificity as well as the advantage of not using nephrotoxic contrast. However, the presence of metal clips produces artefacts in the images which hinders their interpretation.

Definitive diagnosis is made by means of arteriogram, which also enables an initial therapeutic approach with percutaneous angioplasty, with or without the insertion of an expandable prosthesis. Should endovascular dilation be unsuccessful, graft revascularization is indicated via new anastomosis with the internal iliac artery or a synthetic graft.

The treatment of kidney artery stenosis depends on both the symptoms and the degree of obstruction and is therefore not justified in cases with controlled hypertension, stable kidney function or stenosis under 40% of artery span.

Arterial thrombosis

Renal vascular pedicle thrombosis is a rare complication which presents in 1% of cases, with arterial thrombosis in 0.55%.

The literature describes several factors associated with graft thrombosis: right kidney, history of venous thrombosis, diabetic nephropathy in the recipient, technical problems (vascular torsion, stenosis, atheroma plate detachment, etc.) and pre-operation haemodynamic status. The onset of vascular thrombosis (arterial or venous) in patients without any technical explanatory factors means we have to rule out the presence of any thrombophilic condition that might justify the onset of this pathology.

The debut of arterial thrombosis is characterized by the sudden onset of oligoanuria and is diagnosed by means of Doppler ultrasound, arteriogram or gammagraphy, with an absence of graft perfusion.

The immediate consequence of arterial thrombosis is hot ischaemia of the graft. A thrombectomy can be attempted to treat and repair the origin of the clot's onset. However, despite such efforts, patients usually require transplantectomy due to a period of excessive ischaemia that makes the graft unrecoverable.

In the event of re-transplant, patients with a history of arterial thrombosis should undergo thromboembolic prophylaxis, which gives results equal to those of primary transplants.

Venous thrombosis

The onset of venous thrombosis occurs in 0.5% of transplants and is also related to technical failures (anastomosis stenosis, torsion, folds, etc.). Although it may be secondary to venous compression due to collections, the origin remains unknown in most cases.

Symptoms of oligoanuria with abdominal swelling, pain and haematuria associated with worsening kidney function or absence of function lead us to suspect venous thrombosis. The Doppler ultrasound will show an inversion of diastolic flow due to the increase in venous pressure. With angiography, venography and gammagraphy with technetium, one can appreciate contrast or radiotracer capture by the kidney without elimination via the venous circuit.

Kidney viability will determine the treatment to follow. The presence of kidney infarction indicates transplantectomy; however, a thrombectomy may be attempted in the case of partial thrombosis associated with anti-coagulating treatment with intravenous (IV) heparin sodium.

If associated with thrombosis of iliac vessels, consider insertion of a vena cava filter and the need for anti-coagulating or surgical treatment. A complication that may occur after venous thrombosis is the appearance of a pulmonary thromboembolism due to clot migration via the vena cava.

Arteriovenous fistula

Arteriovenous fistulas in a transplanted kidney have an incidence between 0.5% and 16% and are almost always acquired. The most frequent ones are iatrogenic fistulas after fine needle aspiration renal biopsy.

The most common clinical symptoms are alteration of graft function, haematuria and HBP which may give rise to left heart failure, although 70% of fistulas are asymptomatic. During auscultation, a continuous murmur is appreciable over the kidney graft, due to uninterrupted blood flow from the artery to venous circulation. You can see the fistula as a region within the parenchyma with flow increase via Doppler ultrasound, although definitive diagnosis is via arteriogram.

Most arteriovenous fistulas close spontaneously. In the event of fistula persistence or serious symptoms, selective embolization by means of interventional radiology will be the first therapeutic option. Should this be inefficient, open surgery should be considered to perform fistula resection, partial nephrectomy or even transplantectomy.

Kidney artery aneurysm

This exceptional pathology consists of a kidney artery span dilation that includes all the wall layers. These aneurisms can be of several kinds. They may have been transferred with the transplanted kidney and remained unnoticed, be secondary to a technical failure or due to infection of the arterial artery (mycotic aneurysm).

Aneurysms secondary to technical failure are pseudoaneurysms (dilation of an artery without all of its layers), which is because the suture does not include all the artery layers. This type of aneurysm is usually asymptomatic; however, the major complication, which has exceptionally bad prognosis, is spontaneous rupture that requires urgent surgical revision.

Infectious aneurysms are due to an infection of the arterial walls and produce symptoms on rupture that require urgent surgical treatment, usually consisting of a transplantectomy.

An aneurysm already present in the extracted kidney is usually asymptomatic. During bench surgery we can resect the aneurysm sac and suture the edges of its neck; or resect the artery segment where the aneurysm is and insert a graft to replace the arterial defect. Should the aneurysm go undetected it is usually diagnosed during the kidney graft vascular study and requires expectant management.

Haemorrhage

Onset of haemorrhage occurs in 1.9% of transplants and is most frequent in transplants with multiple vessels. It is related to vascular anastomosis dehiscence. Diagnosis may be clinical (abundant exit of haematic material through drainage or wound tumefaction with a drop in haematocrit) or via MRI (collections). If bleeding is active or collection is important, surgical revision is indicated.

3.3. Lymphocele

This is an accumulation of lymphatic liquid in a non-epithelized cavity that appears in the retroperitoneal cavity newly formed for the implant between the iliac vessels and pelvic wall. It is the most frequent fluid collection post-kidney transplant; however, its incidence is difficult to determine due to different detection criteria and methods. It has been described in between 1.1% and 58% of cases.

The physiopathology of lymphocele is not accurately known, although there appears to be a direct relationship to dissection of the lymphatic vessels surrounding the iliac vessels. Other factors that intervene are the increase in lymphatic flow secondary to diuretics, acute rejection, type of immunosuppression (mTOR inhibitors) and obesity.

The importance of lymphocele principally depends on its volume and the compression it may exert on different structures: altered kidney function if the parenchyma is compressed, urinary tract dilation, difficulty of venous return if the pedicle is compressed, oedema of lower ipsilateral limb if iliac vessels are compressed, etc.

Should a collection of renal peritransplant fluid be suspected, perform imaging tests (ultrasound and/or CT) to determine volumes, location, etc. Precise diagnosis requires analysis of the liquid obtained to identify its origin (urine *vs.* lymph). With lymphocele, the creatinine levels in the liquid obtained are similar to plasmatic levels.

The treatment of lymphocele is indicated if the patient presents any kind of symptom. There is a debate regarding the first therapeutic option. Percutaneous drainage has a 33% recurrence, after which a sclerosing agent is instilled (povidone iodine at 10%) with recurrence of up to 25%.

If these treatments are ineffective, marsupialization is indicated, and for some groups this is the treatment of choice. It consists of opening a window in the peritoneum so that the peritoneal membrane absorbs the liquid accumulated.

Keyhole surgery is the technique of choice for marsupialization, although open surgery is recommended for patients requiring additional transplant surgery that cannot use the minimally invasive surgery approach. Recurrence is around 6% and related to obstruction of the peritoneal window.

CONCLUSIONS

» When evaluating the viability of a kidney graft, the most used tool is the operating theatre examination to evaluate the appearance of kidney perfusion and the presence of lesions. In addition, other tools may be used (histological assessment with cryobiopsy, risk scores, use of perfusion machine resistive index, etc.), but there is no consensus about their usefulness, and we currently do not have sufficient evidence to exclusively rely on any tool when taking decisions.

» In kidney transplantation, surgical aspects are as important as the medical approach. Meticulous surgical procedure with the appropriate technique in each case is of the utmost importance. Likewise, being aware of any complications that might appear post-surgery is vital to prevent and deal with any that arise.

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TOPIC 2 - Unit 3

Postoperative

ORGAN TRANSPLANTATION

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INTRODUCTION

There is no doubt that current kidney transplant (KT) results are better in comparison to those of the 1980s. There are many reasons for this improvement in graft survival: surgical advances, more efficient immunosuppressive drugs, better clinical treatment of patients, in addition to new advances in diagnosis and the treatment of posttransplant complications.

A major factor in long-term kidney graft survival is to achieve the best possible kidney function during the initial post-KT period. Factors related to kidney function in the short term are donor age, pre-existing lesions in the donor kidney, delayed graft function, urological complications, acute rejection, surgical factors, medical complications or pharmacological nephrotoxicity.

In practical terms, a distinction is made between premature dysfunction (first 3 months post-KT) and late dysfunction (from month 3).

Early kidney graft dysfunction is defined as alterations occurring during the first 3 months (12 weeks) post-KT.

We distinguish 2 stages in this period:

1. The immediate post-KT period (week 1). Alterations in the kidney graft are essentially due to acute tubular necrosis, although surgical reasons may also lead to acute rejection for high immunological risk patients.
2. The early post-KT period (weeks 2-12). Medical and immunological complications.

This unit refers only to premature dysfunction of the kidney graft.

1. PREMATURE GRAFT DYSFUNCTION

These alterations occur within the first 3 months post-KT. This is the most delicate period of a kidney transplant since it has been proven that the kidney function obtained at the end of this stage has prognostic implications regarding long-term kidney graft survival.

Table 1 shows the major causes of kidney dysfunction during this period.

Table 1. Major causes of posttransplant kidney dysfunction

Immediate post-KT period (0-1 week)
Delayed graft function or acute tubular necrosis (ATN)
Haemorrhage
Kidney graft artery or vein thrombosis
Urinary tract stenosis
Urinary fistula
Acute rejection due to T cells
Acute rejection mediated by antibodies
Pharmacological nephrotoxicity or iodine contrast
HUS or FSGS recurrence
Urinary infection
Primary graft dysfunction
Early post-KT (1-12 week)
Acute rejection due to T cells
Acute rejection mediated by antibodies
Pharmacological nephrotoxicity or iodine contrast
Infections due to BK virus (BKV) or cytomegalovirus (CMV)
Urinary infection
Urinary tract stenosis
Kidney artery stenosis
Lymphocele
Recurrence of kidney disease

1.1 Immediate posttransplant period (first week post-KT)

After KT surgery the kidney graft can evolve in 3 ways:

1. Immediate kidney function: kidney graft presents with immediate diuresis and rapid improvement in kidney function.
2. Delayed kidney graft function: Known classically as acute tubular necrosis (ATN), which is a histological lesion, characterized by the presence of anuria or oliguria requiring dialysis (anuric ATN) or post-KT diuresis without kidney function improvement (ATN with conserved diuresis). Delayed graft function is the most frequent cause for kidney dysfunction and appears in 20-30% of KTs globally, although its frequency is highly variable depending on KT characteristics. It is an infrequent event in kidney transplantation from a living donor (<5%) and very frequent in kidney transplantation from a deceased donor after cardiac death (≥40%). After a period of 1-4 weeks the kidney graft recovers its function. In large numbers of patients delayed graft function has been associated with worse kidney function one year after KT, a greater acute rejection risk and worse kidney graft survival. Nevertheless, there are many individual cases where the recovered ATN has no negative consequences for the evolution of the kidney graft. The following section will explain this in greater detail.
3. Primary graft dysfunction: Defined as a kidney graft which will never function and is uncommon (less than 1%). It can be difficult to establish surgical causes, which may include bad kidney preservation, severe ATN, kidneys from donors with expanded criteria or acute kidney failure.

1.2 Early posttransplant period (1-12 weeks post-KT)

During this period, factors producing alterations in kidney function may be of a different kind, although one of the most important is acute rejection in its different forms.

Other reasons are obstruction of the urinary tract, nephrotoxicity, acute pyelonephritis, kidney artery stenosis or some recurrence of kidney disease.

2. REASONS FOR PREMATURE DYSFUNCTION OF A KIDNEY GRAFT

The first weeks after transplantation are the most significant in determining the long-term outcome of the transplanted graft. Factors related both to the donor and the recipient can determine outcome.

As more grafts are used from donors with an important cardiovascular risk, diabetes and extended age, or from donors after cardiac death (DCD), these factors can have a direct impact on graft function in the short and longer term. On the recipient side, immunological and infectious elements in particular can have a direct impact on immediate graft function. In addition, the side effects of immunosuppressive drugs can directly influence outcome.

2.1 Acute tubular necrosis

Acute tubular necrosis (ATN) is one of the main reasons for 'delayed graft function', which generally manifests as oliguria/anuria with need for dialysis immediately post-KT. It may also appear with less intensity as conserved diuresis without a drop in creatinine levels. Global frequency is 20-30% of all KT, although this depends on the type of KT. Table 2 provides details of the risk factors for presenting with ATN.

Incidence can be up to 70% in DCD KT. However, in a living donor KT with highly reduced cold ischaemia time, the frequency is extremely low (under 5%). The duration of ATN is variable and in most cases the kidney graft recovers function in 1-2 weeks, although it may take up to 4-6 weeks. Delayed graft function is an important risk factor since it has been associated with lower kidney function and lower graft survival. It also increases the risk of presenting acute rejection due to a greater expression of HLA antigens during the kidney tubule regeneration process. A differential diagnosis of acute kidney failure should be conducted (Table 3).

Table 2. Aetiology of acute tubular necrosis or delayed kidney graft function

DONOR	RECEIVER	SURGICAL
Asystole donor	Prolonged dialysis	Prolonged cold ischaemia
Brain-dead deceased donor	Retransplant	Prolonged hot ischaemia
Elderly	Complicated surgery	Euro-Collins > Wisconsin
Kidney failure	Cardiovascular instability	
Cause of death: stroke	Dehydration	
Severe atheromatosis	Severe atheromatosis	
Cardiovascular instability		
Heart attack before extraction		

Table 3. Aetiology of acute kidney failure according to cause

Aetiology
Pre-renal: Dehydration, ICV, hepatic cirrhosis, anasarca, sepsis
Vascular: Autosomal recessive disease, renal artery thrombosis, renal vein thrombosis
Kidney: ATN, acute rejection, acute interstitial nephritis (infectious, pharmacological), glomerulonephritis (recurrence, *de novo*), haemolytic-uremic syndrome, nephroangiosclerosis
Pharmacological: Nephrotoxins (NSAIDs, aminoglycosides, contrast), pharmacological interactions
Urological: Stenosis (ureterovesical, ureteral, pyeloureteral), lithiasis, extrinsic compression (lymphocele)

2.2 Hyperacute rejection

Currently, this is highly infrequent due to the compulsory crossmatch test before transplant, which must be negative. When hyperacute rejection occurs, it is due to the existence of high pre-existing donor-specific antibodies at the time of KT or incompatibility of ABO blood groups. It is diagnosed immediately after unclamping in surgery. The kidney graft becomes cyanotic and finishes with irreversible thrombosis.

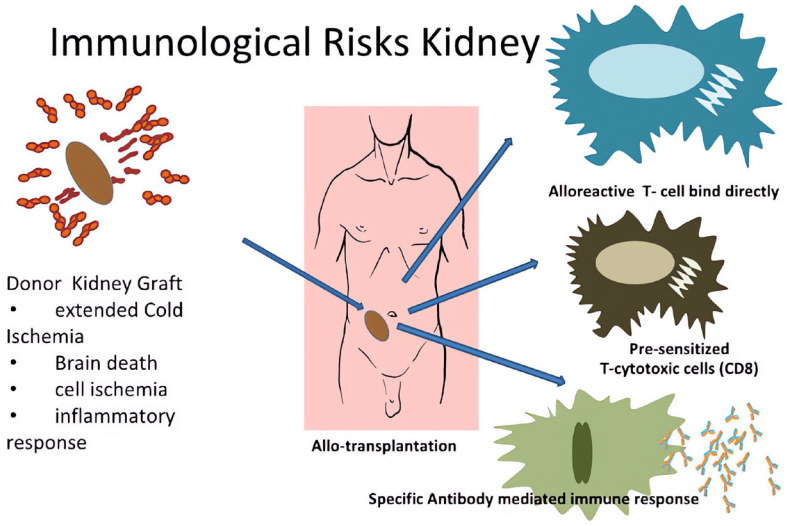

Figure 1. Hyperacute rejection.

2.3 Acute rejection mediated by T cells

This type of rejection is due to activation of T lymphocytes which consider the kidney graft antigens as foreign. Cell immunity activation occurs in different stages. Firstly, the recipient's (signal 1) T lymphocytes recognize the donor's alloantigens. Presentation of the donor's antigens to the recipient's T lymphocyte may be direct (recipient's T lymphocytes recognize the donor's foreign HLA peptides in the donor's presenter antigen cells, or indirect (recipient's T lymphocytes recognize the donor's foreign HLA peptides processed by the recipient's antigen presenter cells). Next co-stimulation via T lymphocyte CD28 is required. This joins the recipient's CD80 and CD86 of the antigen presenter cells. Finally, clonal expansion of T lymphocytes (signal 3) occurs.

Acute rejection is most frequent in the first 3 months after KT, although it may occur at any time after transplantation. Clinical symptoms are highly variable depending on the severity of rejection. It may manifest as a simple asymptomatic deterioration of kidney function or have great clinical expressivity (oliguria, graft pain, graft enlargement, fever). The kidney ultrasound shows findings suggestive of pyramidal oedema, enlarged graft, cortico-medullar differentiation loss or an increase in resistance indices.

A kidney biopsy is necessary for definitive diagnosis. Currently the international Banff classification used worldwide is extremely useful since it provides a detailed description of the different rejection types (Table 4).

The frequency of acute rejection is variable. In non-hypersensitized patients, frequency is low (10-15%), whereas in immunological risk patients, frequency is over 50%. Risk factors for acute rejection include the presence of anti-HLA antibodies, poor immunosuppression, low HLA compatibility, insufficient treatment adherence, young age, HIV positivity, Black ethnicity, retransplant, ATN post-KT or CMV infection. Response to treatment is over 80%. **An incomplete treatment response or the late onset of acute rejection has a negative impact on long-term graft survival.**

Table 4. Banff 97 classification

1	Normal
2	Antibody-mediated changes Due to documentation of circulating anti-donor antibody, C4d, and allograft pathology C4d deposition without morphologic evidence of active rejection Acute antibody-mediated rejection Chronic active antibody-mediated rejection
3	Borderline changes
4	T-cell mediated rejection (TCMR) Acute T cell mediated rejection (Type/Grade) IA. IB. IIA. IIB. III. Chronic active T cell mediated rejection
5	Interstitial fibrosis and tubular atrophy, no evidence of any specific aetiology Mild interstitial fibrosis and tubular atrophy (<25% of cortical area) Moderate interstitial fibrosis and tubular atrophy (26%-50% of cortical area) Severe interstitial fibrosis and tubular atrophy/loss (>50% of cortical area)
6	Other

Source: Banff 97 classification (updated 2009 and 2013); Haas M. AJT 2014;14:272-83.

2.4 Acute rejection mediated by antibodies

Also known as acute humoral rejection. This rejection is mediated by donor-specific HLA antibodies generally due to prior sensitization caused by transfusions, previous transplants or pregnancies (donor specific antibodies or DSA). The appearance of antibodies against other donor antigens (MICA, endothelium, minor HLA or AT2 recipient antigens) may also trigger it. It is considered an important reason for premature and late kidney dysfunction.

Diagnosis is established based on 4 criteria:

1. Deterioration of kidney function.
2. Detection of antibodies against donor antigens (DSA).
3. C4d deposit on peritubular capillaries under immunofluorescence.
4. Characteristic histological lesions, especially capillaritis in peritubular or glomerular capillaries.

Although C4d is a typical finding of this rejection, very recently the new Banff criteria were modified in order to diagnose rejection in the absence of C4d deposits. Acute rejection generally appears in the first months after kidney transplant, although in high immunological risk patients with high DSA levels it may occur prematurely in the first weeks after KT. It is characterized by a rapid deterioration of kidney function. In 80-90% of cases it responds to treatment but may recur and frequently evolves to chronicity.

2.5 Urological complications

Vascular complications

- Haemorrhage
- Kidney artery or vein thrombosis
- Iliac artery thrombosis
- Kidney artery stenosis
- Aneurysms and pseudoaneurysms

Urinary tract complications

- Haematuria
- Urinary fistula (vesicoureteral, ureteral or pyelic)
- Urinary tract stenosis (ureterovesical, ureteral or pyeloureteral)

Perirenal collections

- Lymphocele
- Bruising
- Abscess
- Urinoma

Surgical wound complications

- Infections: superficial or deep infection, cellulitis, abscess
- No infection (cutaneous, superficial dehiscence, incisional hernia, evisceration, serous)

Urinary infection

Lithiasis

Tumours

2.6 Nephrotoxicity by anticalcineurinics (cyclosporine or tacrolimus)

Cyclosporine and tacrolimus are nephrotoxic drugs causing kidney hypoperfusion via vasoconstriction of afferent arterioles. This causes a drop in kidney plasma flow and glomerular filtering. Immunosuppressive strength and acute nephrotoxicity are inseparable.

Initially, the symptoms are reversible; however, if maintained over time they may produce a chronic irreversible effect. Severe contraction and persistence of arteriole muscle cells may cause characteristic histological lesions, such as arteriolar hyaline lesions. Maintained chronic hypoperfusion would cause glomerulosclerosis with interstitial fibrosis and tubular atrophy.

Clinical manifestations of nephrotoxicity due to anticalcineurinics are:

1. Acute nephrotoxicity (reversible deterioration of kidney function).
2. Chronic nephrotoxicity (irreversible deterioration with histological alteration).
3. Thrombotic microangiopathy.
4. Hydroelectrolytic alterations (metabolic acidosis with hyperchloraemia, hyperpotassaemia and hypomagnesaemia).

A kidney biopsy in acute nephrotoxicity may present alterations like:

1. Isometric vacuolization in kidney tubules.
2. Inclusion bodies (megamitochondria, autophagolysosomes).
3. Tubular microcalcifications.

In chronic nephrotoxicity histological findings are:

1. Interstitial fibrosis in bands.
2. Arteriolar hyalinosis.
3. Glomerulosclerosis.
4. Tubular atrophy.

Calcineurin inhibitor-associated thrombotic microangiopathy is the maximum expression of nephrotoxicity, characterized by microangiopathic haemolytic anaemia (schistocytes, thrombocytopenia, elevation of LDH and reduction of haptoglobin). It must be differentiated from severe acute rejection and aHUS. The biopsy detects a thrombotic microangiopathy with intraglomerular clots. However, it must be noted that thrombotic microangiopathy can have many different causes apart from calcineurin inhibitor toxicity.

2.7 Pharmacological nephrotoxicity

In early post-KT, pharmacological nephrotoxicity may occur that causes a deterioration of kidney function. The most common nephrotoxic drugs are aminoglycosides, NSAIDs, amphotericin B, ACE inhibitors, ARBs, iodine contrast.

Pharmacological interactions with cyclosporine/tacrolimus must be carefully monitored. Drugs that induce CYP4503A4 (rifampicin, phenobarbital, hydantoins, NNRTIs) increase the metabolism of cyclosporine/tacrolimus, which may trigger rejection. Conversely, CYP4503A4-inhibitors (verapamil, diltiazem, fluconazole, clarithromycin, PIs) reduce the metabolism of cyclosporine/tacrolimus which may cause severe nephrotoxicity.

As with other patients, in kidney transplants an acute interstitial nephritis can also appear, which should be suspected in the presence of eosinophilia.

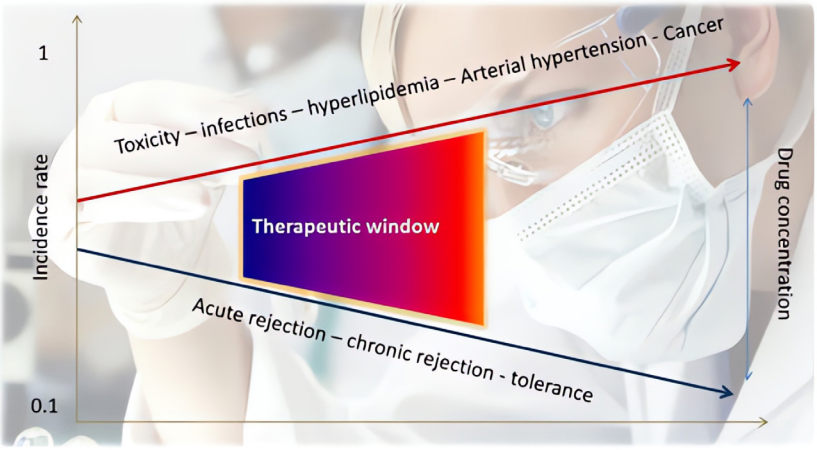

Figure 2. Therapeutic window.

2.8 Recurrence of nephrological disease

All glomerular diseases may recur to a greater or lesser extent in a kidney transplant. However, there are two types which may be responsible for premature kidney graft dysfunction: focal segmental glomerulosclerosis (FSGS) and aHUS.

Focal segmental glomerulosclerosis (FSGS)

The primary type may recur prematurely in 50% of cases. Premature recurrence risk factors are children, rapid evolution to terminal CKD and a premature recurrence in a previous KT. FSGS causes a serious deterioration of kidney function accompanied by nephrotic range proteinuria. Prognosis is unfavourable with a 50% graft loss. Treatment consists of plasma exchanges, which should be carried out early.

Atypical haemolytic-uraemic syndrome (aHUS)

This may be idiopathic or familial. It is due to an alteration in complement regulation. In half of the cases, the mutation is detectable (factor H, factor I or in MCP). Mutations of Factors H or I have a high recurrence risk (over 80%) and are associated with a high rate of graft loss. The treatment currently administered is eculizumab, which has modified its natural history favourably.

3. DIAGNOSTIC TOOLS FOR KIDNEY TRANSPLANT ASSESSMENT

During the early posttransplant period, common sense is required in the diagnosis of kidney graft dysfunction. The clinical history and a physical examination are particularly important. The existence of diarrhoea or vomiting and signs of dehydration suggest prerenal acute kidney failure.

Sudden onset of anuria suggests obstruction of the urinary tract or a vascular pathology. Kidney ultrasound is a very useful technique since it enables various causes to be ruled out. Different complementary tests will be performed pursuant to clinical suspicion.

Kidney ultrasound

A basic technique for kidney graft assessment. Examination is in B Mode and Duplex-Doppler. It enables assessment of echo-structure, kidney size, analysis of intra-renal perfusion (resistance and acceleration indices), examination of vascular anastomosis and urinary tract assessment. It also enables detection of peri-renal collections (Figure 3 and Figure 4).

In acute rejection, although its sensitivity is low, an ultrasound can aid diagnosis. Ultrasound findings are kidney volume over 30%, pyramidal oedema, loss of cortico-medullar differentiation, thickening of kidney pelvic wall, elevation of IR to over 0.80.

In kidney artery stenosis, a Doppler ultrasound is extremely useful and has enormous diagnostic sensitivity. Ultrasound findings are PSV >2–2.5 m/s, post-stenosis turbulence, IA <3 m/s2, IR <0.50 and Doppler wave tardus-parvus morphology.

Recently, the contrast-enhanced ultrasound (CEUS) has become a very useful technique in kidney transplant in different situations such as focal perfusion defects (polar artery lesion), cortical necrosis or the diagnosis of kidney artery thrombosis and is particularly helpful in assessment of kidney ganglions (Figure 5).

Computed tomography (CT)

A contrast CT enables identification of a kidney ganglion. An angio-CT is indicated to confirm diagnosis of kidney artery stenosis, an aneurysm or pseudo aneurysm and in diagnosing a post-surgical haemorrhage (Figure 6).

Radioisotope renography

This technique, also known as a nuclear renal scan, consists of injecting 5 mCi of Tc^{99m} MAG3. It is simple, non-invasive non-nephrotoxic, non-allergic and low-cost. An analogical image and an activity/time curve are obtained. This technique is essentially used during the initial post-KT period for patients presenting with anuria ATN. It is a functional examination, reporting the degree of radioactive drug incorporation and enables monitoring of kidney graft although anuria.

Curve morphology and the intensity of capture provide 3 basic types of curves: Curve Type 1, with third stage presence (which may be delayed); Curve Type 2, progressively ascending; and Curve Type 3, vascular curve or curve with an initial low amplitude peak in the first minute dropping rapidly. This last curve indicates severe ATN and is predictive of a slow recovery of kidney function.

Kidney biopsy

This technique enables histological diagnosis of renal parenchyma alterations. We currently have the periodically updated international Banff classification that enables classification of the different lesions detected in a kidney transplant. (Table 4) describes the general outline of this classification, but the details of each type are beyond the scope of this Unit.

In simple terms, in acute rejection mediated by T cells, an infiltrate of mononuclear cells appears which, depending on the intensity of rejection, may affect the interstitial, tubules, or vessel walls (Figure 7 and Figure 8). In acute rejection mediated by antibodies, essentially capillarity or infiltrate of poly-morphonuclear cells appear in the peritubular or glomerular capillaries accompanied by a C4d deposit in the peritubular capillaries visible in the immunofluorescence study (although recently this finding has become unnecessary) (Figure 9).

Pyelography via nephrostomy

Indicated with findings of hydronephrosis of the kidney graft in the ultrasound and requiring placement of a nephrostomy (Figure 4). Contrast can be injected through this to diagnose the cause of the obstruction (ureteral stenosis or ureterovesical junction).

Cystography

Indicated when a vesicoureteral fistula is suspected or there is a diagnosis of reflux or obstruction of the lower urinary tract.

Arteriography

Indicated in the treatment of kidney artery stenosis to perform an angioplasty and placement of a stent in the artery.

Other studies

There are other diagnostic techniques applicable that depend on clinical suspicion. Urodynamics are indicated in functional bladder diseases.

Cytology and cystoscopy are required to examine haematuria. When studying the kidney graft ureter, we can use a CT urography, catheterization or ureteral neomeatus and evaluation with retrograde pyelography or directly via ureterorenoscopy. A study of the prostatic pathology can be conducted via urological examination, PSA, transrectal ultrasound, flowmetry, and more recently via prostatic NMR.

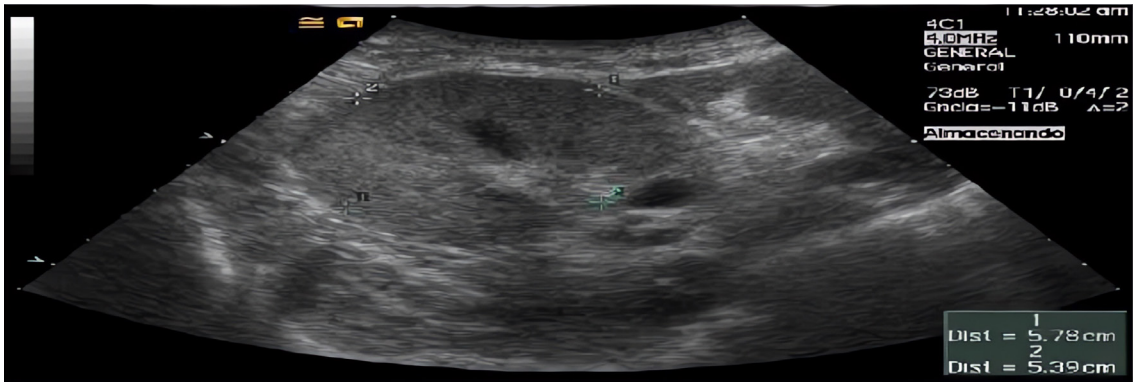

Figure 3. Kidney graft ultrasound (1).

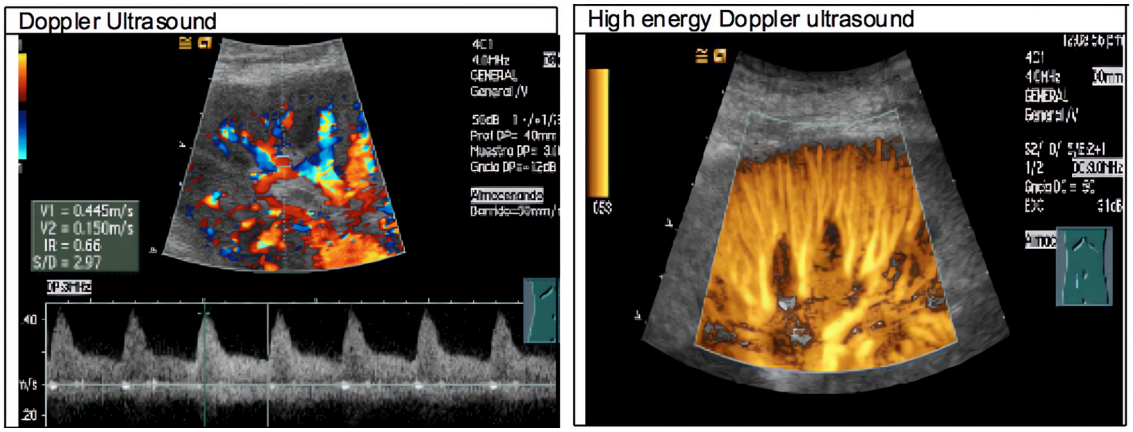

Figure 4. Kidney graft ultrasound (2).

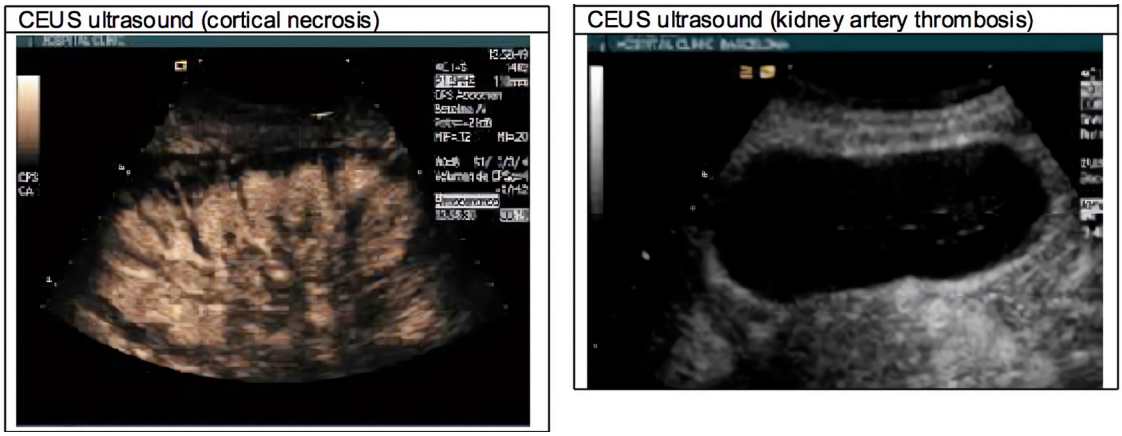

Figure 5. Kidney graft ultrasound (3).

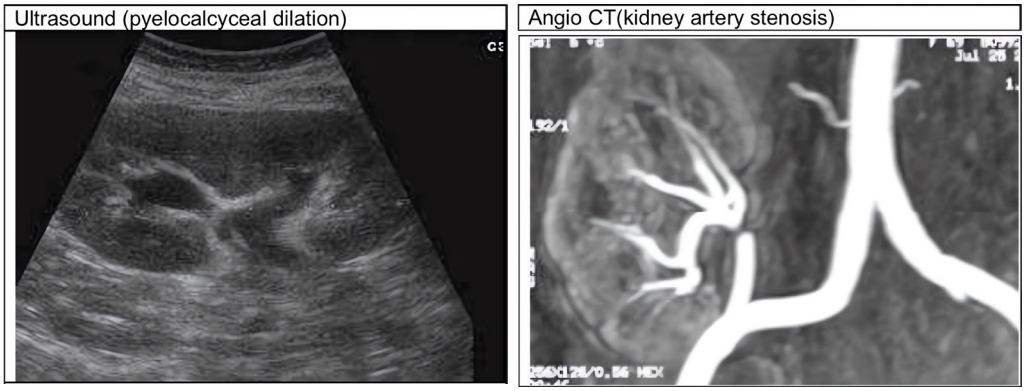

Figure 6. Kidney graft ultrasound and angio-CT.

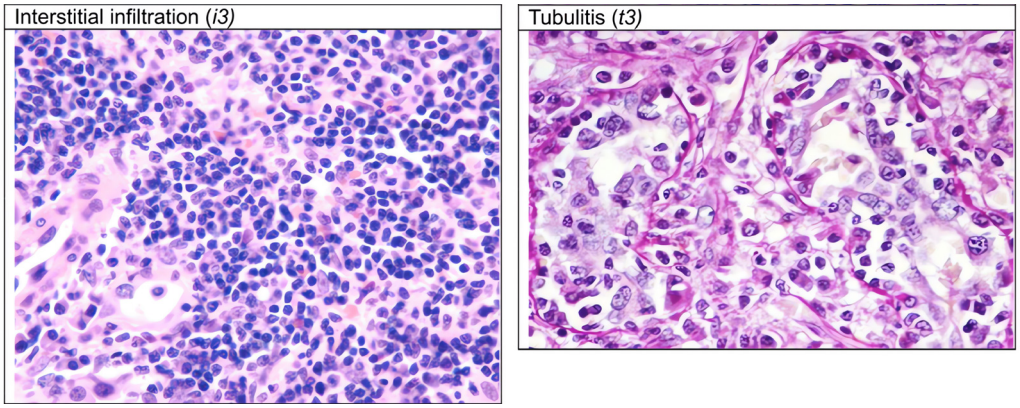

Figure 7. Acute rejection histology (1).

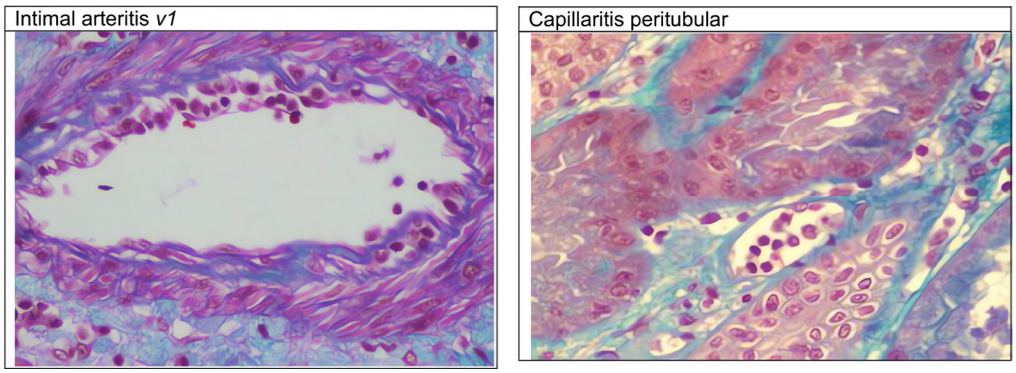

Figure 8. Acute rejection histology (2).

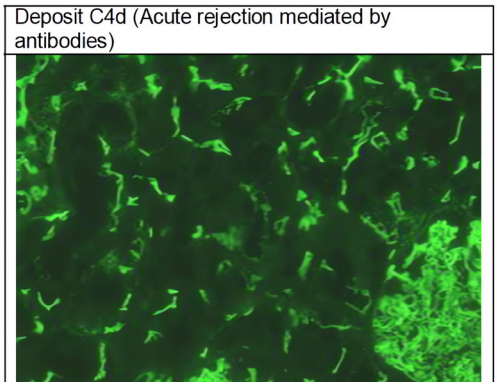

Figure 8. Acute rejection histology (2).

4. TREATMENT OF PREMATURE KIDNEY GRAFT DYSFUNCTION

4.1 Acute tubular necrosis (ATN)

In anuria, the treatment for ATN is haemodialysis, to be maintained until the kidney graft recovers function. It is important not to conduct excessive ultra-filtering in order to avoid intravascular depletion delaying recovery. If the kidney graft has not recovered its function after 2 weeks, a kidney biopsy is necessary to rule out acute rejection. At this stage the kidney requires frequent monitoring with a renal Doppler ultrasound or radioisotope renography. A kidney biopsy should be performed when there is a worsening of these tests or kidney graft dysfunction persists 2 weeks after KT.

4.2 Acute rejection mediated by T cells

Acute rejection treatment depends on the type and severity, in accordance with Banff classification.

1. First level

Methylprednisolone bolus (500 mg x 3 doses) in acute rejection mediated by T cells grade IA, IB, IIA. Treatment response occurs in 70% of cases. When there is no response, rejection is considered cortico-resistant and moves up a level.

2. Second level

Polyclonal antilymphocyte antibodies (Thymoglobulin® or ATG- Fresenius® in cortico-resistant rejections or in rejections IIA, IIB and III.

3. Third level

Acute rejection mediated by antibodies has a specific treatment consisting of eliminating circulating antibodies against the donor (plasmatic exchanges), blockage of new antibody production (rituximab) and immunomodulation of the immune system (polyclonal immunoglobulins). Treatment guidelines vary from centre to centre. In our hospital treatment consists of: antiCD20 monoclonal antibodies (Rituximab - 2 doses 400 mg) + plasmatic exchanges (6-10 sessions) + hyper-immune gamma globulin (200 mg/kg x 3).

4. Fourth level

Rescue treatment of acute rejection mediated by antibodies. The efficacy of these treatments is debated. Bortezomib and eculizumab have been used.

Bortezomib is a proteasome inhibitor used to treat multiple myeloma that causes apoptosis of plasmatic cells. An intravenous dose of 1.3 mg/m2 is used in combination with plasmatic exchanges.

Eculizumab is a humanized monoclonal antibody against a C5 fraction of complement, approved in treating nocturnal paroxysmal haemoglobinuria and aHUS. Treatment guidelines for rejection are not well established. Guidelines similar to those for HUS are used, with a weekly dose of 900 mg (4 doses) followed by 3 doses of 1200 mg every 2 weeks. Reuse combined with plasmatic exchanges and rituximab.

4.3 Nephrotoxicity due to cyclosporine/tacrolimus

Treatment consists of reducing dosage. In cases of severe nephrotoxicity like thrombotic microangiopathy, treatment must be suspended. Combined treatment with mycophenolate should be boosted to avoid a reduction of immunosuppression that triggers acute rejection.

CONCLUSIONS

» The initial evolution after KT is essential for long-term kidney transplant results. It is vital to achieve the best possible kidney function in the first 6 months post-KT. Factors related to short-term kidney function are: donor type (deceased or living), donor age, deceased donor's cause of death, donor's kidney biopsy, delayed graft function, urological complications, acute rejection, surgical factors, medical complications or pharmacological nephrotoxicity.

» Delayed graft function, surgical complications and acute rejection are the most important causes of premature kidney graft dysfunction. Delayed graft function or ATN appear in 20-30% of cases although frequency is variable depending on transplant characteristics. During ATN the kidney graft must be correctly monitored, and an early kidney biopsy should be conducted to rule out the addition of acute rejection. Immunological alterations of rejection are complex and require accurate histological diagnosis. The Banff classification has enabled homogenization of different rejection types and provides extraordinary value in generating scientific evidence between the different transplant teams. Knowledge of the physiopathology of acute rejection has enabled better indication of treatments available.

» Today humoral immunity with antibody formation against the donor plays an ever-increasing role in kidney graft dysfunction. There are different levels of treatment depending on the type of rejection.

» **Nephrotoxicity due to anticalcineurinics may also product premature kidney graft dysfunction. Correct dosage of these drugs has reduced the incidence.**

» Urological complications, particularly of the urinary tract (stenosis or fistulas) and to a lesser extent vascular complications also contribute to premature kidney graft dysfunction. There are some infrequent nephropathies which may recur during the initial kidney transplant stage, such as aHUS or primary FSGS.

» Early diagnosis of premature kidney transplant dysfunction is essential. A detailed medical history with analytical parameters enables an initial approximation. Ultrasound and kidney biopsy are two essential techniques. Other techniques like isotopic renography, CT, NMR, or arteriography may be used depending on the initial suspicion.

» **Early diagnosis of premature kidney transplant dysfunction is essential.**

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TOPIC 3 - Unit 1

Indications and waiting list

ORGAN TRANSPLANTATION

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INTRODUCTION

Death due to liver disease is the 12th cause of death in the United States and in Europe. Every year 40,009 patients die, there are 750,000 hospitalizations, and 2,000 cases of sudden acute liver failure are recorded in the USA [1,2]. A liver transplant is a technique that enables increased patient survival and improves quality of life for patients with certain liver diseases at specific stages.

Eligibility for transplant not only depends on the pathology, such as cirrhosis, but also on the specific moment when a transplant becomes indicated. Liver transplant survival at 1, 3 and 5 years is 85-90%, 75-80% and 65-75% respectively [3]. Therefore, it is offered for health conditions that have a lower survival than the survival expected after liver transplantation.

This unit describes the indications for accepting patients as transplant recipients, taking into account the imbalance between available donors and recipients.

The aims of a liver transplant are to prolong survival and improve quality of life, optimizing the use of organs. According to the European Liver Transplant Registry (ELTR) over 7000 liver transplants were performed in Europe in 2013.

1. INDICATIONS FOR LIVER TRANSPLANT

A patient should be considered eligible for a liver transplant as a treatment for:

» end-stage liver disease (ESLD);

» primary liver tumours, as an oncologic curative treatment;

» genetic/metabolic systemic diseases for which liver transplantation halts the disease.

In addition to two other conditions:

a. Life expectancy per year is lower than that offered by a transplant.

b. No alternative therapy with similar outcomes can be offered.

Therefore, when evaluating a prospective liver transplant candidate, the following questions should be asked:

» Is there an alternative treatment for their liver disease?

» Can the patient survive the operation and postoperative period?

» Are there comorbidities that limit transplant survival and make it inappropriate?

» Can the patient follow the treatment regime and postoperative follow-up?

» Is the recurrence rate of their disease acceptable after liver transplant? [4]

There are a series of liver diseases for which liver transplant is indicated. Depending on the pathology, the indication for transplant or otherwise depends on different criteria. Cirrhosis in itself is not an indication to perform a liver transplant. However, decompensated cirrhosis implies short survival, making a liver transplant desirable. Compensated cirrhosis is associated with survival that is similar to or even better than liver transplantation. Hence, although life expectancy is lower than for the general population, transplant is not considered in this stage of the disease.

There follows a list of the different pathologies which lead to transplant and their indication criteria. Table 1 includes the different groups of pathologies and Figure 1 shows the frequencies of these pathologies that lead to transplant in accordance with ELTR data. Currently, the most common indications in adults are liver cirrhosis, essentially due to hepatitis C (HCV) and alcohol, and hepatocellular carcinoma. However, direct antiviral agents against HCV are dramatically decreasing its prevalence and non-alcoholic steatohepatitis is rising as a common cause of liver disease.

Table 1. Biliary complications after liver transplantation

Hepatic cirrhosis
Viral (HCV, HBV)
Alcoholic
Autoimmune
Cryptogenic
Chronic cholestatic diseases
Primary biliary cirrhosis (PBC)
Sclerosing cholangitis (SC)
Secondary biliary cirrhosis
Severe acute liver failure (acute liver failure)
Acute hepatitis
Hepatotoxic drugs/toxins
Genetic and metabolic disorders
Hereditary haemochromatosis
Wilson´s disease
AAT deficiency
Nonalcoholic fatty liver disease (NAFLD)
FAP
Caroli´s disease
Collagen vascular disease type I
Cystic fibrosis
Polycystic disease
Primary hyperoxaluria
Protoporphyria

Tumours
Primary: FHCC, haemangioendothelioma, cholangiocarcinoma
Metastatic: Neuroendocrine tumours (NET)
Hepatic vascular diseases
Budd-Chiari syndrome
Veno-occlusive disease (VOD) or SOS

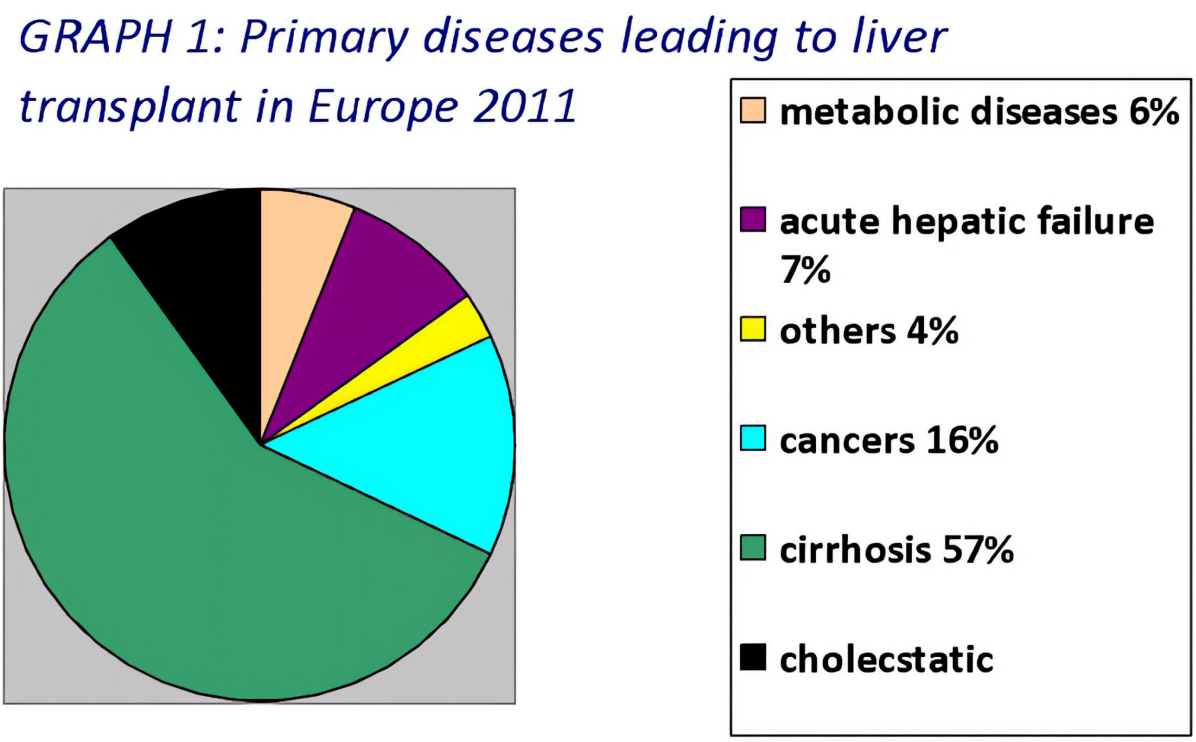

Figure 1. Primary diseases leading to liver transplant in Europe.

1.1 Hepatic liver cirrhosis

As already mentioned, for ESLD a transplant is indicated when life expectancy without a transplant is less than 90% at 1 year. How can this expected survival be calculated? The Child-Turcotte-Pugh and MELD scores are used for chronic ESLD.

The Child-Turcotte-Pugh[5] scale has 3 stages depending on the resulting score, A (5-6 points), B (7-9) and C (10-15), with 1-year survival of over 90%, 85-95%, and 50-85% respectively. Only B and C patients may be considered for transplant (Table 2).

Table 2. Child-Turcotte-Pugh Scores

Measurement	1 point	2 points	3 points	Units
Bilirubin (BR) (total)	<34 (<2)	34-50 (2-3)	>50 (>3)	µmol/l (mg/dl)
Serum albumin	>3.5	2.8-3.5	<2.8	g/l
INR / PT	<1.7 / >50	1.7-2.3 / 30-50	>2.3 / <30	Without unit / %
Ascites	Absent	Mild	Moderate-Severe (Refractory)	Without unit
Hepatic encephalopathy	Absent	Grade I-II	Grade III-IV	Without unit

MELD [6,7] is a mathematical model based on serum creatinine figures, bilirubin levels and INR. MELD=3.78 (serum total bilirubin in mg/dl) +11.2 (INR) +9.57 (serum creatinine mg/dl) +6.43. The MELD score varies between 6 and 40 points, corresponding to a 3-month survival of 90% and 7% respectively. As explained in the next unit, MELD is also used to prioritize waiting list patients. A liver transplant indication corresponds to a MELD >15 [8].

Any of the complications appearing in the following (Table 3) indicate the need for a liver transplant, since they are associated with a significant drop in survival.

Table 3. Complications indicating need for a liver transplant

Complications of cirrhosis
Ascites refractory to treatment
Chronic bleeding due to portal hypertension gastropathy
Encephalopathy
Hepatocarcinoma
Variceal haemorrhage
Liver synthesis deficit
Metabolic diseases with systemic manifestations
AAT deficiency
Familial amyloidotic polyneuropathy (FAP)
Glycogen storage disease (GSD)
Haemochromatosis
Primary hyperoxaluria
Systemic complications of chronic liver disease
Hepatopulmonary syndrome
Portopulmonary hypertension (PPHT)

1.2 Hepatic tumours

These include hepatocarcinoma, cholangiocarcinoma and metastases of neuroendocrine tumours (NET). Due to the high recurrence rate of cholangiocarcinoma only patients with early-stage tumours that are unresectable due to associated liver disease or anatomical location are considered after a specific oncologic protocol that includes surgery and chemotherapy. These patients should therefore only undergo transplantation in selected centres with well-established treatment protocols for this tumour, which means that there is a very low applicability of liver transplantation for these tumours [9].

The indication of liver transplantation for hepatocellular carcinoma should use the Barcelona Clinic Liver Cancer (BCLC) algorithm. According to this staging, liver transplantation should be offered for patients who meet the Milan criteria [10].

The Milan criteria include patients with a single tumour under 5 cm or maximum of three tumours each under 3 cm, without extrahepatic disease, because they reach a 75% survival rate at 4 years and tumour-free survival of 83%. Tumour dimensions must be measured using CT or MRI. Some centres include patients with tumours that exceed the Milan criteria (San Francisco criteria, Up-to-seven criteria). However, extending tumour dimensions beyond Milan criteria survival will increase tumour recurrence and decrease patient survival [11].

1.3 Chronic cholestatic liver diseases

When is the right time to indicate a transplant? It is the same as for any advanced liver disease. For certain diseases, like sclerosing cholangitis and primary biliary cirrhosis, there are specific diagnosis models which indicate the time for inclusion on the waiting list. One of these is the Mayo Clinic model, which includes age, bilirubin, albumin, PT and oedema [12]. Inclusion criteria also accept untreatable pruritus and recurring cholangitis in primary sclerosing cholangitis (PSC) or sepsis as transplant criteria [13].

1.4 Acute liver failure

Another important indication for liver transplant is acute liver failure, which may be due to viral infections or intoxications. Evaluation is different for these patients. There are two methods used to evaluate which livers can recover alone, which indicate transplant, and which must be transplanted. The criteria used are Clichy [14] and King's College [15]. Lately, MELD is also being used to evaluate these patients. (Table 4)

Table 4. King's College, Clichy and MELD criteria

KING´S COLLEGE
Paracetamol intoxication
pH <7.3 on admission and 24 hour stay
Or the following 3 criteria:
Encephalopathy grade 3-4
Serum creatinine >3.4 mg/dL
INR >6.5 (PT >100 seconds)

Acute liver failure not associated with paracetamol
INR>6.5 (PT >100 seconds)
Or the following 3 criteria:
Hepatitis non-A non-B or idiosyncratic reaction to drugs
Under 10 or over 40 years
PT >50 seconds
Serum bilirubin over 18 mg/dL
Interval between onset of jaundice and onset of encephalopathy greater than 7 days
CLICHY
Any of the following regardless of FHF aetiology:
Encephalopathy grade III or IV and factor V <30%
Factor V under 20% in patients under 30
Under 30% in patients over 30
MELD
Over 30

1.5 Hereditary and metabolic disorders

Alpha-1antitrypsin (AAT) deficiency may lead to cirrhosis with its complete range of complications. A lung screening must be performed to rule out associated lung disease [16].

Haemochromatosis may also lead to cirrhosis, so the indications are those of a chronic liver disease. We must bear in mind that iron deposits may affect myocardial tissue and cause arrhythmias. Furthermore, there seems to be greater association with hepatocellular carcinoma (HCC) than in other aetiologies of cirrhosis [17].

Wilson's disease causes copper accumulation in the brain, liver and eyes. This accumulation may lead to chronic liver disease and also to acute liver failure. It is associated with neuropsychiatric dysfunctions, haemolytic anaemia and kidney involvement. The indication will occur with the onset of cirrhosis complications, as with any other aetiology, and acute liver failure [18]. A transplant should not be conducted in an attempt to revert neurological problems due to copper accumulation.

In the case of familial amyloidotic polyneuropathy (FAP), the liver produces mutated amyloid precursors that are deposited in other organs. The liver functions normally, but the amyloid substance essentially causes a motor-sensitive polyneuropathy and autonomic dysfunction. Moreover, it usually causes cardiac, ocular and kidney impairment. A kidney transplant does not alter the cardiac and ocular involvement and detains but does not improve, neurological impairment. Therefore, a liver transplant is indicated preferable for patients under 50 whose neurological system is not severely affected. The livers of these patients may be used as an element in a domino transplant for other recipients, as they are normal and complications derived from amyloid deposits take over 10 years to develop [19].

Primary hyperoxaluria type I (PH1) is due to a hepatic synthesis defect causing oxalate accumulation. Damage is essentially at kidney level, with onset of terminal kidney failure between 20-40 years old. A liver transplant is possible in patients with good kidney function or combined with a kidney transplant in terminal kidney failure cases [20].

1.6 Vascular liver diseases

Suprahepatic vein occlusion disorders or hepatic sinusoid obstruction, if not resolved via aggressive anticlotting therapy, may result in acute liver failure leading to a transplant.

1.7 Patient evaluation

Selection process

The evaluation and selection process for liver transplant candidates is exhaustive, requires a thorough study and should search for comorbidities that will need treatment before transplantation or which contraindicate a transplant.

The following table summarizes the 2013 transplant guide for the USA.

Table 5. 2013 USA Liver Transplant Guidelines

2013 USA Liver Transplant Guidelines	
Financial screening	Secure approval for evaluation.
Hepatology evaluation	Assess disease severity and prognosis, confirm diagnosis and optimize management.
Surgical evaluation	Confirm need for transplant, identify technical challenges (e.g., prior abdominal surgery, portal vein thrombosis, etc.), discuss donor options (deceased, living, expanded criteria).
Laboratory testing	Assess hepatic synthetic function, serum electrolytes, renal function, viral serologies, markers of other causes of liver disease, tumour markers, ABO-Rh blood typing, creatinine clearance, urinalysis and urine drug screen.
Cardiac evaluation	Initial non-invasive evaluation with echocardiography. Non-invasive stress testing and cardiology evaluation if cardiac risk factors are present (hyperlipidaemia, hypertension, diabetes, cigarette consumption, age >60 years).
Hepatic imaging	Doppler ultrasound to document portal vein patency, triple-phase CT or gadolinium MRI for tumour diagnosis and staging.
General health assessment	Chest X-rat, Pap smear and mammogram (women), colonoscopy if patient is age 50 years or older, or has PSC.
Dental assessment	Identify dental caries, buried roots and dental abscesses. Coordinate dental extractions, if necessary, with hepatology.

2013 USA Liver Transplant Guidelines	
Anaesthesia evaluation	Required if unusually high surgical risk, i.e., patient has portopulmonary hypertension (PPHT), hypertrophic obstructive cardiomyopathy, previous anaesthesia complications.
Psychiatry, psychology or mental health professional consultation	Determine whether there is history of substance abuse, psychiatric illness, or adjustment difficulties (e.g., behavioural or adherence problems).
Social work evaluation	Address potential psychosocial issues, adequacy of support, and possible effect of transplantation on patient's personal and social system.
Financial and insurance counselling	Itemize costs of transplantation and posttransplantation care, review insurance coverage, help develop financial management plans.
Nutritional evaluation	Assess nutritional status and patient education.
Infectious disease	Identify infectious processes that require intervention prior to transplant (e.g., latent TB or posttransplant e.g., CMV-*naïve* recipient).
Adapted from O'Leary JG, Lepe R, Davis GL. Indications for liver transplantation. Gastroenterology. 2008;134:1764-1776.	

Liver transplant contraindications

The following table summarizes transplant contraindications.

Table 6. Contraindications for liver transplant

Liver transplant contraindications
Severe heart or lung diseases or conditions
Active alcoholism or drug addiction
AIDS with high viral charge and low CD4
Hepatocellular carcinoma (HCC) with metastatic disease
Uncontrolled sepsis
Intrahepatic cholangiocarcinoma
Malignant extrahepatic disease
Acute liver failure within PIC >50 mmHg o PPC <40 mmHg
Hemangiosarcoma
Persistent noncompliance
Lack of family/suitable social support
Anatomic abnormality impeding transplant

Choosing the right timing for inclusion on the waiting list is subject to debate, depends on the prognosis of the liver disease and on the probability of liver transplantation after inclusion on the waiting list. For these reasons, the criteria may vary in each country or region. However, in general, inclusion on the waiting list comes with a MELD greater than 12-15 or Child>7 in patients with decompensated ESLD. More or less restrictive criteria may apply depending on the availability of donors.

Finally, several years ago, the maximum age for transplant was considered to be 65; Currently, the limit is less clear, and has even been indicated for patients over the age of 70 with good results [21]. The general condition and comorbidities of the patient play a major role in this decision. Again, each country or region may determine their own specific ages.

2. WATING LIST

Waiting lists for liver transplantation are the consequence of an imbalance between the increasing number of potential liver transplant recipients and available liver donors. Governments, healthcare providers and stakeholders have endeavoured to find different ways to reduce the waiting lists. Attempts to increase the number of organs include heightening public awareness of donation, promoting live donation, liver partition, and donation after cardiac death.

Over the past 20 years, most countries have recommended that the deceased-donor waiting list be prioritized according to disease severity and risk of mortality. This strategy is designed to provide patients waiting for a liver with equal access to organs and prioritize access to transplantation for those with greatest medical need [22].

Historically, most liver transplant programmes, including UNOS (the United Network of Organ Sharing), used time and the Child-Turcotte-Pugh (CTP) scale to prioritize waiting lists into 3 categories: 3 (7-9 points on CTP), 2B (over 10) and 2A risk of dying within 7 days [23]. The CTP model seemed to be good at predicting patient death; however, it has several disadvantages, namely:

- Empirical component selection
- Arbitrary use of cut-off points for quantitative variables
- Equal importance of all variables within the model
- Imprecise cut-off points for qualitative variables
- Exclusion of important prognostic factors such as creatinine

Later, the Mayo Clinic developed the Model for End-Stage Liver Disease (MELD) score to evaluate the prognosis of cirrhotic patients after transjugular intrahepatic portosystemic shunt (TIPS) placement. This score uses INR, serum creatinine and serum total bilirubin. After its evaluation in a large cohort of patients with end-stage liver disease it demonstrated a good prognostic performance to predict the risk of mortality within 3 months. After this validation, in February 2002, UNOS adopted MELD as the criteria to prioritize patients. The inclusion of clinical variables did not increase the predictive value of this scale, which is objective and reproducible [24].

However, MELD has some flaws i.e., certain circumstances, such as dehydration, the use of diuretics, and haemorrhage alter creatinine values. Furthermore, high bilirubin values may also change measurement of creatinine.

The INR value varies between laboratories. This is why variations of MELD have arisen in an attempt to avoid these problems. Some examples are:

MELD-Na (2) MELD + 1,59 x (135 – Na (mmol/L)); Na range = 120 and 135 mmol
MELDNa (3) MELD - Na (mmol/L) – (0.025 x MELD x (140 – Na (mmol/L)) + 140; Na range = 125 – 140 mmol/L
MESO (4) MELD / Na (mmol /L) x 100
iMELD (5) MELD + (age (years) x 0.3) – (0.7 x Na (mmol/L)) + 100
UKELD (6) 5 x {1.5 x ln (INR) + 0.3 x ln (creatinine (µmol/L)) + 0.6 x ln (bilirubin (µmol/L)) – 13 x ln (Na (mmol/L)) + 70}
Updated MELD (7) 1.27 x ln (1 + creatinine (mg/dL)) + 0.94 x ln (1 + bilirubin (mg/dL)) + 1.66 x ln (1+INR)

The incorporation of MELD as the allocation system was associated with a decrease of inclusions on the waiting list and mortality, without worse transplant outcomes [25,26]. Nevertheless, it was also demonstrated that in patients with a MELD score under 15, the mortality rate with liver transplant was greater than for those not transplanted, so it was decided that a minimum MELD of 15 [27] (the so-called Share 15 rule) was necessary for inclusion on the waiting list.

Up to one third of liver transplant candidates have a hepatocellular carcinoma with good hepatic function. Therefore, MELD would not be able to detect the risk of death or drop-out due to tumour progression. Other conditions also have a higher risk of mortality or drop-out despite having a low MELD score:

- Refractory ascites and MELD score <15
- Chronic or recurrent encephalopathy and MELD score <15
- Recurrent gastrointestinal bleeding and MELD score <15
- Hepatopulmonary syndrome
- Portopulmonary hypertension
- Refractory pruritus
- Recurrent bacterial cholangitis
- Budd-Chiari syndrome
- Hereditary haemorrhagic telangiectasia
- Polycystic liver disease
- Familial amyloid polyneuropathy
- Hepatic metastases of a gastrointestinal endocrine tumour
- Other rare liver malignancies

For these patients, MELD exceptions (extra points) were defined. This allocation system requires frequent re-evaluation and updating of the assigned MELD score to ensure equity in the risk of mortality among patients with different aetiologies [28].

In recent years, several published studies have shown that use of MELD has achieved a reduction in waiting list mortality. However, posttransplant morbidity and costs increase [29]. On the other hand, neither biliary complications nor transfusion requirements appear to increase.

CONCLUSIONS

» Evaluation for liver transplant should be considered once a patient with chronic end-stage liver disease has experienced ascites, hepatic encephalopathy, infection variceal haemorrhage or hepatocellular dysfunction results in a MELD score ≥15.

» In a liver transplant candidate potentially treatable aetiologies and components of hepatic decompensation such as ascites, hepatic encephalopathy, or variceal haemorrhage should be treated.

» candidates should undergo age and risk factor-appropriate cancer screening, screened for bacterial, viral, and fungal infections prior to transplant.

» The MELD score is able to accurately predict the mortality on the waiting list.

» For an LT candidate whose MELD score does not adequately reflect the severity of their liver disease, an appeal for MELD exception points should be made.

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TOPIC 3 - Unit 2

Organ evaluation and surgical procedure (techniques and surgical complications)

ORGAN TRANSPLANTATION

INTRODUCTION 148

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2. CONVENTIONAL TECHNIQUES: WHOLE LIVER GRAFTS 152
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INTRODUCTION

This unit describes the process performed to assess potential transplantable livers, current strategies for increasing the number of transplantable organs, the main surgical techniques and the most important short- and long-term surgical complications after liver transplantation.

1. ORGAN EVALUATION AND CURRENT STRATEGIES FOR INCREASING THE ORGAN POOL

Due to the increasing disparity between the number of patients awaiting a liver transplant and the number of available livers, the acceptance criteria for donor livers have increased substantially in the past 20 years. In the early 1990s donors older than 60 years were not accepted for liver transplantation, whereas in the 2010s half of the donors in Europe were older than 60 years. Moreover, donation is not only considered for donors after brain death (DBD) but also for donors after cardiac death (DCD). Despite this extension in the acceptance criteria for donor organs, in particular regarding age, outcomes after liver transplantation are overall similar.

1.1 Organ evaluation

The major limiting factor in liver transplantation is the low number of available organ donors. The transplant community has therefore evolved towards less restrictive criteria for acceptation of a liver graft. Graft survival depends on several factors with a complex interaction:

- **Cause of death:** Stroke and anoxia higher risk than brain trauma.
- **Donor age:** Some authors report a relationship between the use of livers from elderly donors and worse graft survival [1]. However, other studies have demonstrated good results with this type of liver while a low cold ischaemia time is maintained [2,3].
- **Liver steatosis:** Liver steatosis greater than 30% is an independent risk factor for graft loss (relative risk 1.71) [4]. Therefore, it is important to verify hepatic function in blood test results, perform an ultrasound exploration before extracting the organ and even consider waiting for the liver biopsy result before performing the implant.
- **Hypernatremia:** This may be the result of several other factors, including prolonged ICU stay or diuretic treatment of cerebral edema caused by a brain stroke. Nevertheless, studies have linked hypernatremia with a higher degree of early graft dysfunction [5].
- **Cold ischaemia time (CIT):** After the procurement of the organ, cold storage is used to minimize ischaemic injury. Graft CIT is defined as the interval from initiation of donor *in vivo* cold organ preservation to removal of the graft from 4°C cold storage. Cold ischaemia times exceeding 12 horas are associated with higher recipient mortality [6].
- **ABO mismatch:** Donor ABO livers are matched with the recipient ABO. In urgent liver transplantation due to fulminant hepatitis, ABO donor-recipient mismatch is an acceptable option to avoid recipient death, although it carries lower 1- and 5-year graft and recipient survival [6,7].

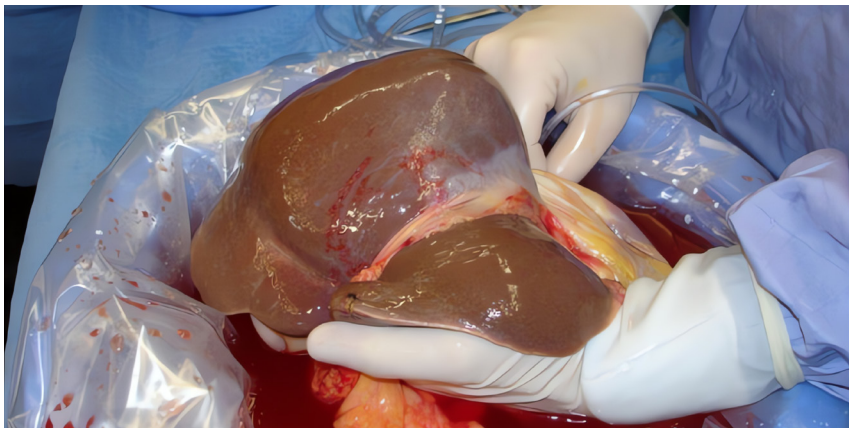

Figure 1. Liver pancreas graft en bloc wash-out at the bench table.

1.2 Strategies for increasing the organ pool

Despite the most common type of liver donor being a whole liver graft from a DBD donor, other options are used to overcome the lack of donors.

1.3 Whole liver graft donation

1.3.1 Donation after cardiac death (DCD)

This is use of a whole liver graft from a donor who has suffered an irreversible cardiac arrest.

The use of DCD attempts to address the acute shortage of organs and to decrease waiting list mortality. There are two methods of organ procurement for DCD: donation after controlled cardiac death, with planned withdrawal of ventilator and organ-perfusion support in the face of catastrophic illness (Maastricht classification class III), or donation after uncontrolled cardiac death, which follows unexpected cardiopulmonary arrest and/or unsuccessful resuscitation (Maastricht classification classes I, II, and IV).

In contrast to liver grafts from standard DBD donors, for which blood circulation and organ perfusion are maintained by the beating heart until initiation of organ preservation, organs from DCD donors are subjected to a period of absence of blood flow before cold preservation can be administered. Diminished quality and function of DCD liver grafts after transplantation have been attributed to an additional warm ischaemic insult that augments organ preservation injury [8,9].

1.3.2 Domino liver transplantation

Given the shortage of deceased donor grafts, domino liver transplantation has the potential to increase the offer for certain patients. The donors are patients who undergo liver transplantation because they have a genetic disease that produces an abnormal protein, leading to amyloid deposition. Patients with this disease, Familial Amyloid Polyneuropathy (FAP) or Corino de Andrade's Disease, have a liver that functions healthily, and which may therefore be used as a donor liver [10].

Some reports show a risk of recipients developing the disease 10-15 years after liver transplant. Consequently, domino liver recipients should be older than 55-60 years to minimize this risk.

1.3.3 Partial graft transplantation

The original rationale for using partial graft liver transplantation was a) TTo replace a metabolic deficiency. b) To allow a timely liver transplant for small recipients who would otherwise have to wait a long time to find a small donor. c) To avoid waiting list drop-out by decreasing the waiting time or in countries where deceased donors are not available.

One of the most important conditioning factors for the use of partial grafts is that the volume must be sufficient to maintain metabolic needs. The importance of the correlation between patient and graft weight defined as GRWR (graft-to-recipient weight ratio) is well established. This ratio should be at least 0.8%, i.e., for a patient who weighs 80 kg a minimum graft weight of 700 g is needed.

This problem is associated with adult living-donor liver patients and is usually solved by using the right lobe for transplantation [11].

1.3.4 Auxiliary transplantation

This may provide an alternative in two situations. The first is for patients with acute liver failure, in whom a partial graft is used to provide support for the patient's diseased liver while it recovers [12]. Once the native liver returns to normal function, the graft is removed, and immunosuppression is withdrawn. The

second case is for patients with functional, congenital or metabolic disorders that affect a normal liver. The graft allows correction of the metabolic disorder while avoiding a full liver transplant [13].

1.3.5 Split liver transplantation

This involves dividing a liver graft in two parts and depends on who the intended recipients are.

- If those sharing the graft are an adult and a child, the liver will be divided into a right lobe that also includes also segment IV, and a partial left graft that includes segments II and III [14].
- If the liver is to be divided between two adults, it will be split in two, the right lobe (segments V to VIII) and the left lobe (segments I to IV). The major determinant for this type of transplant is, above all, the size of the recipient left lobe, since this lobe normally has a weight of around 450 g, which means it can only be implanted in patients with a low weight (50-55 kilograms) [15].

1.3.6 Living donor liver transplantation

Living donation is an important source of liver donors in countries without deceased donation. This procedure appeared as a result of the impossibility of transplanting a child with a donor organ of the appropriate size. In Asian countries, especially Japan and Korea, where the deceased donors are few, it is the principal type of liver transplantation [16].

In adults, living donation generally uses the donor's right liver lobe, which comprises segments V to VIII. Right hepatectomy requires meticulous dissection, in which the right hepatic artery, right portal vein, right bill duct and right suprahepatic vein are isolated.

The minimum size of the graft (Figure 3) must be at least 0.8% in order to ensure viability of both patient and graft [11]. Aside from the technical difficulties in the donor hepatectomy, there is a significant morbidity that affects up to one third of donors, and a mortality rate estimated at approximately 0.12% [11].

Furthermore, the recipient procedure is also challenging, due to the size of the anastomoses, especially of the artery and bile duct, which are 3 to 4 mm in diameter. Nevertheless, outcomes are good, and at present are similar to those obtained with whole grafts from deceased donors [17].

2. CONVENTIONAL TECHNIQUES: WHOLE LIVER GRAFTS

A standard liver transplant comprises three steps, each of which has a profound influence on the short- and long-term results of the surgery. These are: extraction of the donor's liver, removal of the recipient's native liver and implantation [18].

2.1 Donor extraction

A midline incision from the xiphoid process to the pubis is performed for assessment of liver aspect and also to exclude occult malignancies, organ injury or sepsis. If the preliminary assessment is correct, a median sternotomy is performed to gain access to the thoracic cavity. Retroperitoneal dissection is performed, with mobilization of the right colon and duodenum. The inferior mesenteric vein is isolated in order to perform pre-cool perfusion [19].

The abdominal aorta is exposed bellow the root of the inferior mesenteric artery. Dissection of the hepatic hilum is performed, identifying the common bile duct and sectioning it at the duodenal border. The gallbladder is opened, and the bile duct is flushed with saline solution. The final manoeuvre prior to cold perfusion is exposure of the supraceliac aorta. At this point, the distal aorta is ligated at the iliac bifurcation and cannulation of the aorta is performed. While the cold perfusion is started, the aortic arch is clamped and IVC-atria venotomy is performed. The abdominal cavity is filled with ice.

During cold perfusion, the aspect of the liver is continually assessed. After cold perfusion finishes, dissection of the hilum is performed, identifying the portal vein, which is sectioned at the junction between the superior mesenteric and splenic vein. The aorta is sectioned, including the origin of celiac trunk and superior mesenteric artery.

The IVC is sectioned just above the renal vein entry. A complete mobilization of the liver is performed, sectioning the diaphragm. The complete dissection of hilum elements and IVC is performed on the back table.

2.2 Native liver removal

The abdomen is normally opened via a bilateral subcostal incision with midline upper extension, known as the Mercedes incision (Figure 2). The falciform ligament is divided, with removal of all collaterals that may bleed through the dissection.

The left triangular and the gastro-hepatic ligaments are divided. A careful dissection of hepatic hilum is performed, starting with hepatic artery identification (which is sectioned above its bifurcation), followed by the common hepatic and the portal vein. After sectioning the portal vein, the anterior aspect of the IVC is exposed. If local conditions permit, a temporal termino-lateral portocaval shunt is performed [20]. This avoids bowel congestion secondary to the portal sectioning (Figure 3).

The right triangular ligament is divided and, with the inferior liver surface completely exposed, the dissection continues on the plane between the IVC and the posterior surface of the liver.

The IVC preservation performed at this stage of the hepatectomy is called the "piggyback technique", and involves the section of all the small drainage veins between the liver to the IVC (Figure 4) [21]. The right hepatic vein is identified, clamped and divided. The middle and left hepatic veins are clamped and divided. Depending on the anatomy, the 3 hepatic veins are normally connected in a common trunk. (Figure 5) (Figure 6)

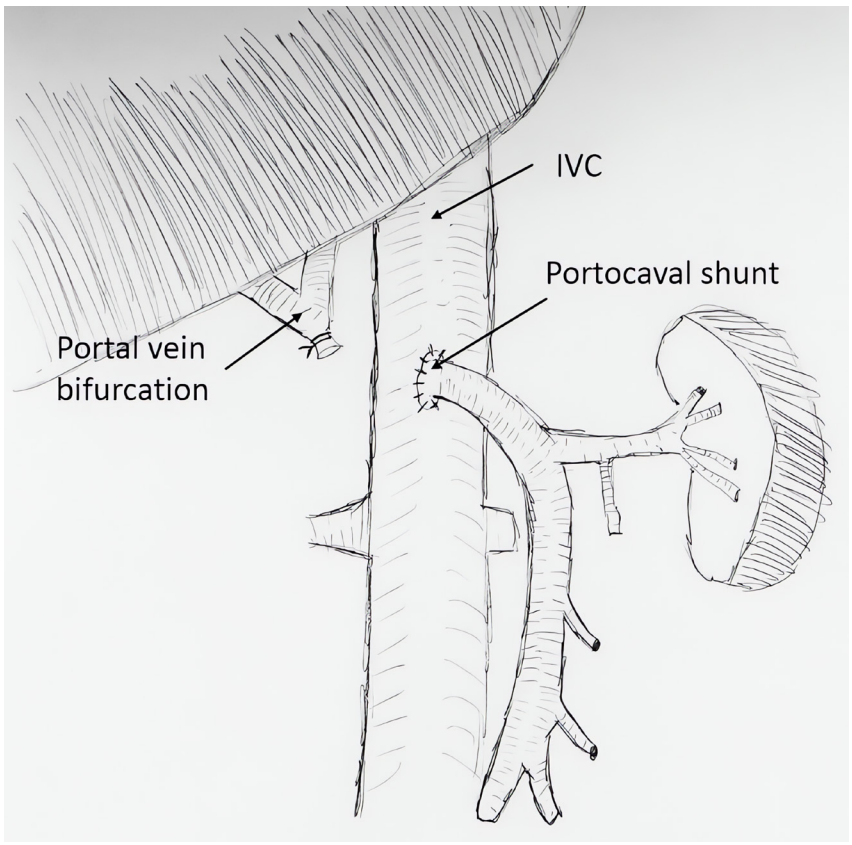

Figure 2. Portocaval shunt.

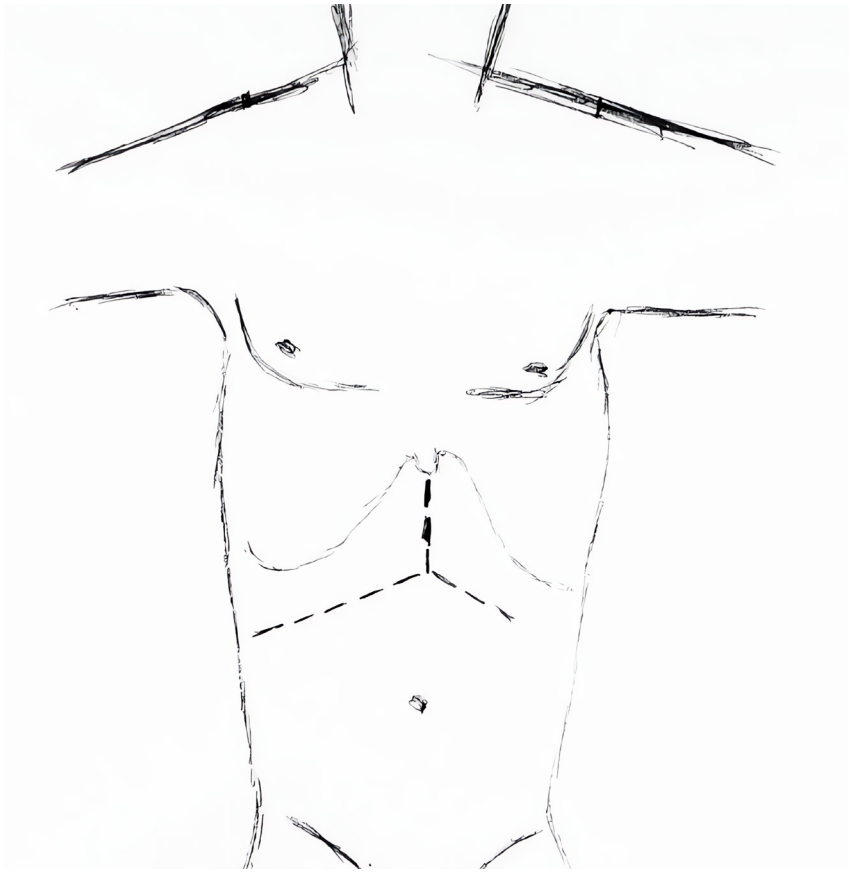

Figure 3. Mercedes incision.

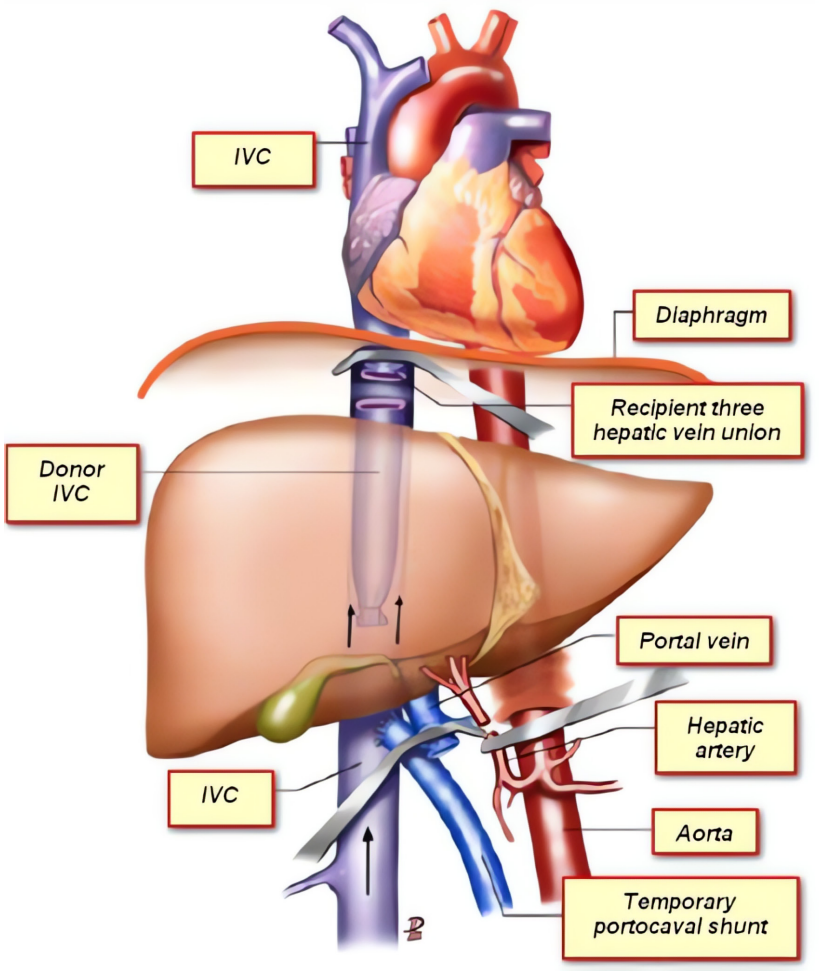

Figure 4. Liver transplantation with "piggyback technique".

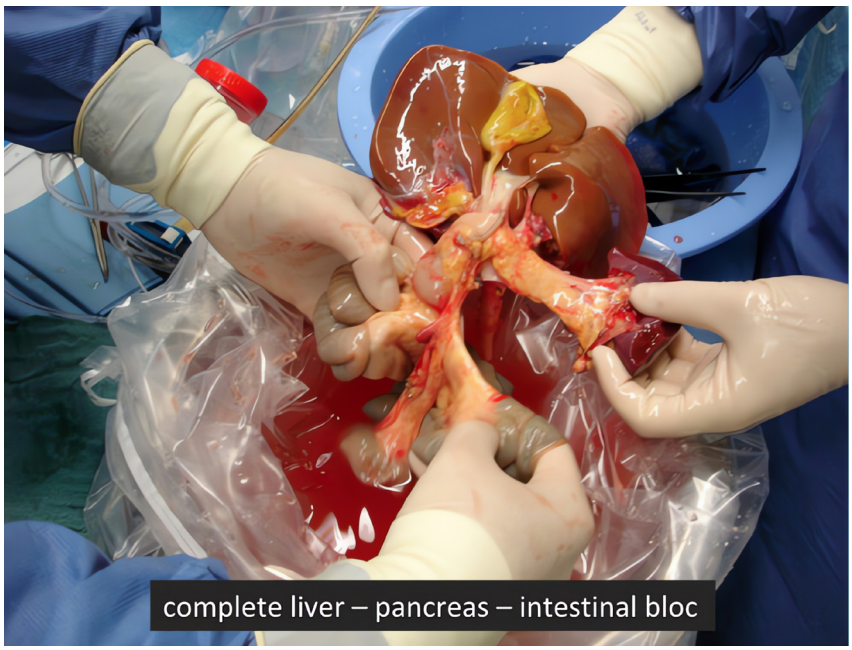

Figure 5. Complete liver – pancreas – intestinal bloc.

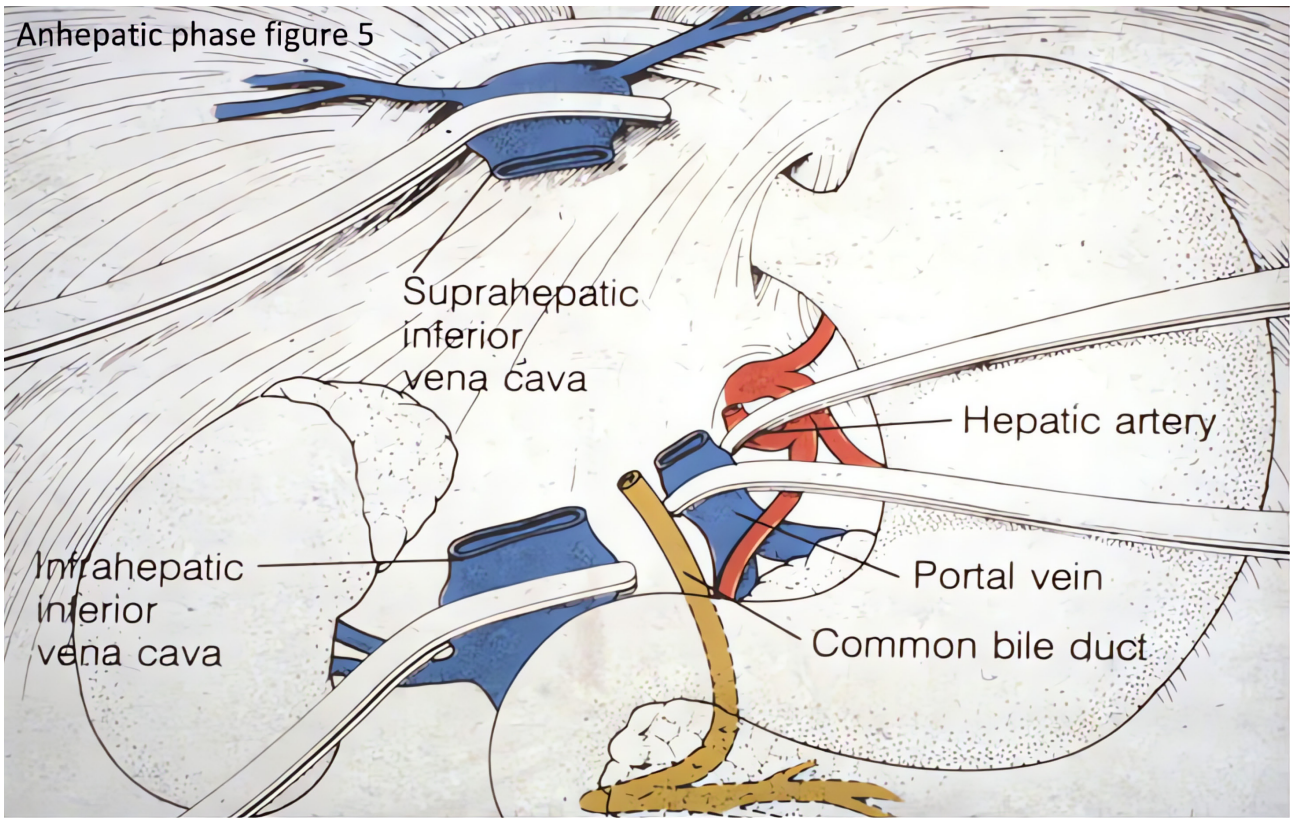

Figure 6. Conventional techniques – Standard liver transplantation. Whole liver grafts.

2.3 Implantation

The liver graft is implanted in the right hypochondrium, in the place formerly occupied by the diseased liver. Anastomosis between the union of the 3 hepatic veins of the recipient and the IVC of the graft is performed. The portocaval shunt is dismounted and portal reconstruction is performed.

In this way, liver reperfusion can go ahead. Hepatic artery reconstruction is a crucial part of the transplant in terms of liver function. It is essential to obtain a large diameter anastomosis and avoid any other factors that could provoke hepatic artery thrombosis in the postoperative period. Finally, the biliary reconstruction is performed, generally in a termino-terminal fashion. Depending on the diameter of the anastomosis, a T-tube may be introduced in the bile duct to prevent local stenosis.

3. SURGICAL COMPLICATIONS

Although the rate of surgical complications has significantly diminished as a result of improvements in surgical technique, instruments and postoperative care, their impact on postoperative progression is still important, both in the short and long term.

Strict assessment criteria in the selection of the right type of recipient (see MELD score Topic 3 unit 1) will reduce uncontrollable preoperative surgical risks and increase immediate transplant outcomes.

3.1 Early postoperative complications

3.1.1 Vascular

3.1.1.1 Arterial

The incidence of hepatic artery thrombosis varies between 1-5%. Its consequences are usually serious requiring reintervention and revascularization in up to 50% of cases, and retransplatation in the rest [22]. The most serious long-term consequence is the occurrence of ischaemic biliary lesions or ischaemic cholangiopathy, which in the majority of cases may raise the issue of retransplantation.

3.1.1.2 Venous

- Vena cava. The piggyback manoeuvre has significantly reduced complications secondary to anastomotic stenosis. Standard incidence is less than 3% [23].
- Hepatic veins. Conversely, preservation of the recipient's vena cava and the need for anastomosis of the 3 hepatic veins initially resulted in the onset of Budd-Chiari syndrome during the postoperative course in up to 30% of the recipients. This complication has been virtually eliminated by performing anastomosis of the 3 hepatic veins or a cavocaval anastomosis.
- Portal vein. *De novo* portal vein thrombosis has a negligible impact. In patients with previous partial or complete portal vein thrombosis, liver transplantation is associated with higher surgical complexity. However, not even complete thrombosis represents a complete contraindication, as there are alternatives for vascular reconstruction, such as the use of the use of the recipient's left renal vein, especially if the presence of a splenorenal shunt is confirmed [24].

3.1.2 Biliary tract

3.1.2.1 Leakage

Biliary leakage is a rare problem which, depending on the cause, has a relatively easy solution, ranging from performance of an endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy, to the temporary placement of a prosthesis. Its incidence is around 5% [25].

In cases of partial grafts, the leak is sometimes found on the raw surface of the split liver and is caused by tubules whose flow progressively decreases. Infrequently, the embolization of these tubules is required, or reoperation is necessary [26].

3.1.3 Haemorrhage

Bleeding during surgery or during the postoperative period occurs in approximately 5-10% of the immediate complications and requires reoperation in 50% of cases. At times, it forces closure of the wound with gauze packing, which then requires reoperation within 48 hours. This method has proven useful in patients with impaired coagulation [27].

3.2 Long-term complications

3.2.1 Ischaemic bile duct injuries

There may be different causes, such as ABO incompatibility, artery thrombosis, ischaemia/reperfusion injury, etc. These injuries are characterized by intrahepatic bile duct strictures and primarily affect their confluence, producing a beaded appearance with stenosis and dilatation along the entire biliary tract. Usual symptoms are cholestasis with intractable pruritus or repeated episodes of cholangitis. The treatment is retransplantation [28].

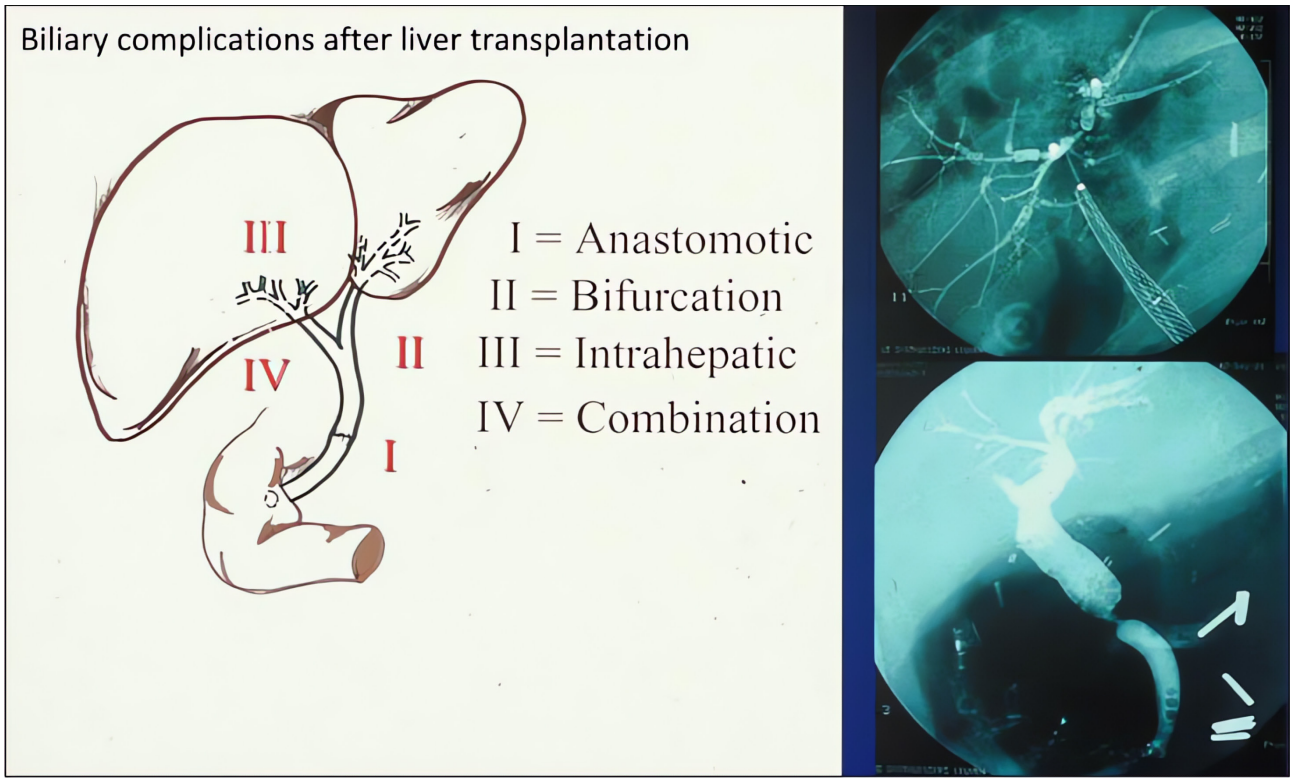

Figure 7. Biliary complications after liver transplantation.

3.2.2 Anastomotic type

Although increasingly rare, anastomotic stenosis is more frequent when performed without a T-tube [29]. Its incidence ranges between 7-10%. The interventional radiology approach has proven effective in a large number of patients who have undergone dilation or stent insertion [30]. In cases without response to such therapies, a hepaticojejunostomy must be performed.

3.2.3 Associated to partial grafts

Recipient. Anastomotic stenosis is one of the major problems of partial liver grafts, with an incidence rate that can reach 50% of recipients (some groups have reported a rate of less than 5%) and although it does not seem to affect long-term survival, it does affect quality of life. Interventional radiology plays an important role in its treatment, through dilation or stent insertion, etc. About 50% of patients require reoperation and the duct-to-duct anastomosis eventually becomes a hepaticojejunostomy [26].

CONCLUSIONS

» Organ evaluation is a complex procedure. Several factors like donor age, hypernatremia, liver steatosis and ABO group are well known to have an important influence in the overall results of a transplant.

» Donation from DBD has reached a steady level. To overcome this limitation, and faced with a severe shortage of organs, DCD livers represent an acceptable option. In order to obtain good results, it is necessary to observe strict time criteria.

» Living donor liver transplantation is a procedure with good results, due to the possibility of transplanting a healthy graft. It is imperative to ensure the lowest possible surgical risk for the donor.

» Liver transplantation techniques have evolved in the last decades. Manoeuvres like the temporary portocaval shunt and the piggyback technique are widely used in transplantation.

» Hepatic artery thrombosis, although infrequent, has serious consequences. In 50% of cases retransplantation is necessary.

» Extensive portal thrombosis does not represent an absolute contraindication to perform liver transplantation.

» Ischaemic bile duct injuries, which appear more frequently in cases with ischaemia/reperfusion injury, provoke cholestasis with repeated episodes of cholangitis. The final treatment is retransplantation.

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TOPIC 3 - Unit 3

Postoperative management and medical follow-up

ORGAN TRANSPLANTATION

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INTRODUCTION

Liver transplant is currently the only curative treatment for patients with irreversible or end-stage liver disease. Posttransplant survival is around 80-90% in the first year, and 70% at 10 years. Survival depends on several factors such as primary disease, recipient status and donor-related factors [1].

Due to the increasing life expectancy of transplant recipients, the goal in management of liver transplantation is not only to ensure patient and graft survival, but to provide good quality of life.

This unit describes the basic clinical and therapeutic principles, and the most common complications that can occur during early and late management of liver transplant recipients.

1. EARLY CLINICAL AND THERAPEUTIC MANAGEMENT

Although liver transplantation is a complex surgical procedure, standardized treatment has resulted in excellent long-term survival and a good quality of life. Outcome is determined by a multi-disciplinary approach of the clinical team in charge of the patient, both in the immediate postoperative period and in the long term.

A well-balanced clinical follow-up with attention to immunosuppressive drug management alongside management of complications and comorbidities will result in excellent long-term results.

1.1 Clinical management

1.1.1 In the Intensive Care Unit (ICU)

Immediately after the transplant, patients are transferred to the ICU. Generally, patients stay 48 hours in an ICU and are subsequently taken to the ward.

The following information should be available on arrival [2,3]:

- **Medical background:** diagnosis and date of the disease, date of inclusion on the waiting list, pretransplant assessment, severity index (model for end-stage liver disease (MELD), Child-Pugh) and other complications related to the disease or other comorbidities.
- **Operation notes:** vascular and biliary anastomosis technique, warm and cold ischaemia, T tube, anaesthetic notes, haemodynamics, intraoperative complications and blood transfusions.
- **Donor and graft data.**

This information will be the basis for treatment, which will include fluid therapy, inotropes, if necessary, gastrointestinal bleeding prophylaxis and antibiotics. The start of immunosuppression depends on the background of both graft and recipient. The aim of management in the ICU is to ensure stabilization, recovery of the patient's vital signs and evaluation of the graft status:

- **Cardiovascular:** Maintain BP (>100-120 mmHg), CVP (4-8 mmHg), PCP (8-10 mmHg).
- **Respiratory:** Early extubation is strongly recommended, SpO_2 >90%, PO_2 100 mmHg, Low FiO_2 and PEEP.
- **Renal and metabolic:** Urine output >1 ml/kg/h for the first 8 hours, >0.5 ml/kg/h after 8 hours and Cr Cl >60 ml/min/1.73 m^2. Glucose, Na, K, Ca, P, and Mg should be also monitored.
- **Neurological function after extubation:** Patients usually recover consciousness immediately after the transplant, but this may be delayed in patients with previous encephalopathy.
- **Nutritional status:** Oral nutrition should be started as soon as it can be tolerated.
- **Blood tests:** Arterial blood gas, biochemistry, clotting, blood cell count, liver function tests, and immunosuppressant levels to be assessed as (Table 1) shows.
- **Radiological tests:** An abdominal Doppler ultrasound scan will be performed in the first 24 hours, followed by another control, usually on the third day. Chest and abdominal X-ray, intraabdominal pressure monitor, and EKG to be performed systematically for the first 72 hours.
- **Control of surgical wound and drainage.**
- **Graft evaluation:** To assess correct functioning of the graft, the following parameters should be evaluated.

Table 1. Blood tests routinely performed for evaluation of the graft recipient

CONTROL	0h	24h	48h	72h
Ions (Na^+,K^+,Ca^2,P), glucose	Yes	q8h	q12h	q12h
Complete blood count	Yes	q8h	q12h	q24h
Coagulation (PT)	Yes	q8h	q12h	q24h
Liver profile (AST; ALT; GPT; Total and direct Bilirubin; GGT; AP)	Yes	q8h	q24h	q24h
Renal profile (BUN; Creatinine)	Yes	q24h	q24h	q24h
Mg+	Yes	q24h	q24h	q24h
Procalcitonin and PCR	Yes	q24h	q24h	q24h
Arterial blood gas	Yes	q8h	q24h	q24h

1) Acid-base equilibrium

Persistent metabolic acidosis is a sign of graft malfunction or infectious disease.

2) Glycaemia

Levels should rise to reach normal ranges by 48h posttransplant. Maintained hyperglycaemia is usually associated with pre-existing diabetes, stress or iatrogenic complications (from corticosteroids or calcineurin inhibitors). Hypoglycaemia is a sign of graft malfunction.

3) Liver function tests

Initial graft function: evaluated by prothrombin activity. In a functional graft, this parameter should usually rise more than 50% at 24-48h.

Ischaemia-reperfusion injury indices: an elevation of transaminase levels after transplant. This is always present as a side-effect of graft preservation and induces an increase of transaminases at 24-48h posttransplant and a decrease thereafter. Early allograft dysfunction is defined as the presence of one or more of the following criteria: bilirubin ≥10 mg/dL on day 7, international normalized ratio ≥1.6 on day 7, and alanine or aspartate aminotransferases >2,000 IU/L within the first 7 days. These criteria predict a higher risk for graft loss and mortality. Persistent levels of AST and ALT may be indicative of severe complications (arterial thrombosis, severe ischaemia-reperfusion injury or acute cellular rejection). The cholestasis profile usually rises around days 10-15 and thereafter slowly decreases.

4) Haemodynamic and vascular monitoring

Prior to the transplant, hepatic disease induces a decrease of peripheral vascular resistance and an increase in cardiac outflow. These parameters should return to normal parameters by day 3 after transplant.

Evaluation of hepatic artery, portal vein and hepatic vein flows: A low portal flow is indicative of a venous permeability complication. The arterial resistive index should be 0.6-0.9. A value below 0.6 is indicative of stenosis or thrombosis, whereas a value over 0.9 points to a secondary oedema due to ischemia-reperfusion injury or a vascular access–related steal syndrome (from splenic or gastroduodenal arteries).

5) Biliary tract function

For patients with a T tube in the biliary tract, production of normal bile indicates good graft function and a cholangiography can be used to evaluate the condition of the biliary tract. The incidence of biliary tract complications in the first year reaches 15-20%.

1.1.2 On the ward

The surgical and medical transplant team, pharmacists, nutritionists, and physical therapists should maintain a close follow-up of the patient [1]. Fluid and electrolyte status, as well as kidney and liver function need to be monitored daily or every other day. Some centres have started an early discharge protocol (<7th day) with acceptable results.

The dosing of immunosuppressive agents should be adjusted according to blood levels and organ function during this period. Liver function test results are monitored for early signs of dysfunction, which can require further studies or intervention. Any major alteration in liver function should trigger a series of studies, which may include a Doppler ultrasound scan to evaluate the vascular patency of the new liver, bile duct studies to evaluate any abnormality of the biliary system, and a liver biopsy to rule out rejection. Based on the findings of these tests, specific treatments are initiated.

1.1.3 Discharge recommendations

In an uneventful recovery, the patient is discharged within 7 to 15 days after transplant and undergoes follow-up as an outpatient. Maintenance medications after discharge include immunosuppressive agents and prophylactic medication to prevent opportunistic infections. In addition to these agents, the patient might also require antihypertensive medication, insulin or oral hypoglycaemic agents, or mild analgesics.

Certain patients require additional medication depending on their original disease. Patients must be instructed to inform the transplant team of any new medication prescribed to them by other physicians in order to assess compatibility with the immunosuppressive agents they are taking. Laboratory studies are usually conducted biweekly for the first 2 weeks, weekly for the next 8 weeks, every other week in the subsequent 2 months, and then once monthly if laboratory test results are stable.

Bloodwork can be done at the patient's local laboratory. The posttransplant coordinator, in conjunction with the transplant surgeon or the hepatologist, should review the outpatient laboratory work.

1.2 Immunosuppression therapy

Immunosuppressive drugs act against the three main events that take place in a rejection [4-6]:

- **Alloantigen recognition:** the antigen-presenting cell (APC) presents donor alloantigens to a recipient T cell by major histocompatibility complex (MHC).
- **Lymphocyte activation (co stimulation):** the APC also simulates other T cell ligands. The T cell receptor (TCR) is then internalized and binds to immunophilin, which stimulates calcineurin. Calcineurin activates the nuclear factor of activated T cells (NFAT), which is translocated to the nucleus and drives IL-2 transcription.
- **Clone expansion:** IL-2 is secreted by T cells, which bind to the IL-2 receptor (IL-2r) on the cell surface by an autocrine mechanism and stimulate lymphoid proliferation.

There are 5 main classes of agents habitually used to induce immunosuppression in liver transplant patients:

1) Steroids (hydrocortisone, prednisone, prednisolone and methylprednisolone)

These drugs suppress leukocyte activity by stabilization of lysosomal membranes and inhibition of the expression of multiple pro-inflammatory genes (cytokines, prostaglandins, leukotrienes, receptors and adhesion molecules) [7]. Steroids remain the first line of initial immunosuppressive therapy and are the first choice for the treatment of acute cellular rejection. However, due to their broad spectrum of side effects (Table 2), it is recommended to taper to zero within 6-12 months after transplant. In cases of autoimmune hepatitis, a minimum dosage should be maintained or combined with other agents, or mycophenolate mofetil (MMF).

2) Calcineurin inhibitors (cyclosporine, tacrolimus)

Calcineurin inhibitors (CNI) inhibit T cell activity by blocking IL-2 transcription, and are key drugs to prevent rejection [8,9]. These drugs are habitually used as early and late immunosuppressive medication in liver transplants. The dosage of calcineurin must be adjusted according to the severity of pretransplant liver disease (MELD or Child-Pugh grades), in monotherapy or in combination with other drugs.

3) Inhibitors of mammalian target of rapamycin (mTOR, sirolimus, everolimus)

These drugs inhibit the T cell proliferation induced by IL-2 by inhibiting the mTOR pathway [10,11].

- **Sirolimus:** Unlike CNI, sirolimus is neither nephrotoxic nor neurotoxic. But, due to its numerous side effects, it should be used as a second line for immunosuppressive therapy in which the use of CNI is not recommended (for example haemorrhage, renal dysfunction or primary graft dysfunction).
- **Everolimus:** This drug increases the risk of hepatic artery thrombosis, for which reason it should not be used until 3 weeks after liver transplantation.

4) Antimetabolites (MMF, azathioprine)

These prevent T and B cell replication by inhibition of DNA and RNA synthesis [4].

- **MMF:** Is neither nephrotoxic nor neurotoxic, and so is usually used as an alternative in cases of CNI-induced or postoperative complications [4,5]. Long-term MMF use can induce bone marrow suppression or gastrointestinal complaints (nausea, vomiting, diarrhoea). These symptoms are usually dose-related and improve with temporary or permanent dose reduction [6].
- **Azathioprine:** This agent can be used as an alternative to MMF (e.g., during pregnancy).

5) Antibodies

Anti-IL2r drugs (basiliximab, daclizumab) inhibit T cell activation by binding to IL2 receptors [4]. These monoclonal antibodies (Ab) can be used in patients with pretransplant renal dysfunction or when glucocorticoid (GC) dose must be reduced [5,6].

Muromonab-CD3 (OKT3). This Ab targets the CD3 T cell receptor, stimulating T cell complement-mediated lysis [4,5]. This monoclonal Ab can be used in cases that require management of steroid-resistant rejection. The initial 2-3 doses induce a cytokine release syndrome (Table 2), which is resolved in 4-6 hours.

Anti-thymocyte globulin (ATG). Induces lymphocyte depletion through complement-dependent lysis and apoptosis. Usually used in cases of steroid-resistant rejection, this polyclonal Ab has multiple T cell targets; therefore, it induces a deep lymphopaenia and plaquetopaenia, which resolves in 3-10 days post administration.

Table 2. Common side effects of immunosuppressor agents used in liver transplants

Agent	Side effects	
GC	Infections	Osteoporosis
	Hypertension	Peptic ulcers
	Dyslipidaemia	Impaired wound healing
	Obesity	Adrenal suppression
	Metabolic syndrome	Neurologic disorders
	Diabetes	Avascular necrosis
CNI (cyclosporine, tacrolimus)	Hypertension	Diabetes
	Acute/chronic renal failure	Hypertension
	Dyslipidaemia	Diarrhoea (>tacrolimus)
	Neuropathy	Electrolyte imbalance (>tacrolimus)
mTOR inhibitors (sirolimus, everolimus)	Hepatic artery thrombosis	Anaemia (microcytic)
	Infections	Peripheral oedema
	Leukopenia	Interstitial pneumonitis
	Thrombocytopenia	Proteinuria
	Hyperlipidaemia	Inhibited wound healing
Antimetabolites (MMF, azathioprine)	Teratogenic	Vomiting
	Bone marrow toxicity	Diarrhoea
	Hepatotoxicity (>Azathioprine)	Abdominal pain
	Nausea	
IL-2r Ab (basiliximab, daclizumab)	Infections	Diarrhoea
	Nausea	Abdominal pain
	Vomiting	Pulmonary oedema / bronchospasm
Anti-CD3 Ab (Muromonab-CD3 (OKT3)	Cytokine release syndrome (fever, diarrhoea, nausea, vomiting, headache, myalgia)	
Anti-thymocyte globulin (ATG)	Infections	Allergic reaction
	Fever	Thrombocytopenia

1.3 Complications

1) Graft-related complications

» Surgical complications (see unit 2)

» Functional complications

Hyperacute and acute cellular rejection

Despite improvements in immunosuppressive therapy, hepatic allograft rejection remains an important cause of morbidity (15-25%) and late graft loss.

Hyperacute rejection is extremely rare. It has been rarely described and is closely related to preformed anti-donor Ab in the recipient (ABO incompatible graft), which bind to antigens on the surface of endothelial cells and hepatic sinusoids of the graft, resulting in complement and coagulation activation leading to massive thrombosis and haemorrhage [12,13].

On the other hand, **acute cellular** rejection mostly occurs between day 7 and days 30-90 after transplant. Risk factors include a low blood immunosuppressant concentration, donor and recipient age, fewer human leukocyte antigen (HLA) matches, prolonged ischaemia time and autoimmune diseases in the recipient. However, this type of rejection may occur late (years) after transplantation.

Clinical symptoms of rejection are highly nonspecific (malaise, fever, abdominal pain, hepatosplenomegaly, ascites and jaundice). Serum analysis shows increased levels of ALT/AST, GGT and bilirubin and PA that do not correlate with the severity of the process. A liver needle biopsy is currently the gold standard for the diagnosis of acute cellular rejection. There are three main histopathological features for the diagnosis of this complication:

» Mixed inflammatory infiltrate (with eosinophils) containing lymphocytes in the portal triad.

» Non-suppurative cholangitis. Presence of destructive cholangitis.

» Endotheliitis. Lymphocytic subepithelial aggregates can be observed. Centrilobular necrosis is indicative of severe acute rejection.

The Rejection Activity Index (RAI) is a scoring system which assesses the grade of severity of the rejection (on a scale of 0 to 9, see Table 3).

Acute cellular rejection should be differentiated from other complications (hepatic artery thrombosis, preservation injury, biliary complications, primary graft dysfunction, septicaemia, HCV, functional cholestasis and massive haemorrhagic necrosis).

Treatment depends on the severity of the rejection. Thus, for severe (RAI 8-9) or moderate (RAI 6-7) acute cellular rejection with severe clinical alterations, the administration of boluses of steroids (1,000 mg/day for 3 days) usually resolves 70-80% of cases [6].

The remaining cases are usually resolved with a second administration. Analytical and histological improvement is evident at day 5 post treatment. In cases of steroid-resistant rejection (10% of cases), administration of OKT3 (5 mg/day, 7-14 days), MMF (1,000 mg/12h) or everolimus may be used as rescue agents.

In cases of HCV, the use of steroids is not recommended. Thus, the increase of CNI or use of an additional agent such as MMF should be considered as alternative approaches. In cases of progression of the chronic rejection, re-transplant should be considered. Patients with moderate acute cellular rejection and moderate clinical alteration (RAI 6-7), or mild acute cellular rejection and mild clinical alteration (RAI 3-5), can be treated by increasing the dose of the immunosuppressant and/or the use of an additional agent [6].

Primary graft dysfunction

Primary graft dysfunction is defined as a biochemical and clinical dysfunction of the graft that almost invariably occurs immediately after liver transplantation [12,13].

The severity of this dysfunction usually correlates with the degree of hepatic injury, and varies from minor, insignificant damage to a primary graft failure. Early graft dysfunction can occur from day 0 to 4 weeks after transplantation due to ischaemia-reperfusion injury or vascular complications.

The pathogenesis of the primary graft failure is unknown. Diagnosis is based on increased AST levels (>5,000 UI/L), coagulopathy (PA <20%), lactic acidosis (pH <7.3), haemodynamic instability and needle biopsy. Re-transplant is usually the only therapeutic option.

2) Medical complications

Infections

Despite the advances in solid-organ transplantation, two thirds of transplanted patients experience some infectious complication after liver transplantation (bacterial 48%, fungal 22% or viral 12%) [3,14,15].

The identification of risk factors (e.g., CMV, donor and recipient serologic status, a presence of underlying infections in the recipient such as herpes virus, TB, HCV, etc., pretransplant colonization of agents resistant to antibiotic therapy) allows the planning posttransplant prevention strategies.

Antibiotic prophylaxis before surgery decreases the risk surgical wound or intraabdominal infection. The most common antibiotic agents are trimethoprim/ sulfamethoxazole (3-12 months after transplant, 3 times/week) for bacterial infections, ganciclovir/valganciclovir for herpesvirus reactivation and fluconazole and liposomal amphotericin B for anti-fungal prophylaxis.

Immunization for CMV (in donor+/recipient- D+/R- and D+/R+ cases), and administration of anti-VZV and herpes simplex virus is also recommended. Transplant patients have a high risk of TB with bad prognosis. Recipients with latent TB infection should be treated, but isocyanide is not well tolerated, therefore they should be closely monitored during treatment.

Infections during the early postoperative period are similar to those described for immunocompetent patients undergoing abdominal surgery (nosocomial infections, particularly focused on the lungs and the abdomen) [15]:

- Intra-abdominal abscesses and secondary peritonitis due to surgical complications (e.g., biliary leakages), caused primarily by enteric pathogens.
- Intra-hepatic abscesses, related to hepatic artery thrombosis.
- Cholangitis, secondary to a stenosis of the biliary tract or obstruction of the drain tube.
- Infection of the surgical wound.
- Nosocomial pneumonias.
- Colitis induced by *Clostridium difficile*.

Acute renal dysfunction

Renal dysfunction is a common complication in the early postoperative course, with a variable incidence (20-85%). Some reports establish a relationship between preoperative renal status and the risk of postoperative complications after transplant [16-17].

Multiple factors originating in the donor, recipient, surgery or drugs can induce preoperative renal dysfunction. Conditions that may affect renal function include pre-existent cardiovascular diseases, surgical technique, volume depletion, hypovolemia induced by anaesthetics, haemodynamic instability, use

of drugs which may affect renal haemodynamics, recipient age, diabetes mellitus. The main cause of postoperative renal dysfunction is related with the use of CNI, usually caused by the dose-dependent vasoconstriction and renal preglomerular dysfunction.

Other factors that induce such dysfunction are primary graft dysfunction or primary graft failure, acute tubular necrosis induced by toxic agents or ischaemia, infectious diseases, etc. The treatment is based on volume reposition, use of diuretics and restriction or discontinuance of nephrotoxic agents [2].

As alternative to CNI, the use of anti-IL-2r Ab in combination with MMF and GC allows a one-week delay in the use of CNI immunosuppressive therapy. Note that mTOR inhibitors should not be used until the third week posttransplant due to an increased risk of hepatic artery thrombosis induced by these drugs. of the vascular complications these drugs can induce. In terms of prognosis, with treatment, 80% of renal dysfunctions can be resolved, but the patients should be closely monitored, due to an increased risk of developing chronic kidney disease.

Neurological complications

The aetiology is often multifactorial and there is a wide spectrum of clinical presentations. Clinical management requires discontinuance of neurotoxic drugs and ruling out structural neurological damage (CT, MRI, lumbar puncture). The most common complications are related to immunosuppressive therapy and include tremors, anxiety or insomnia [2,3,15]. It is usually possible to manage them with medical treatment or by switching immunosuppressive therapy.

Cardiovascular complications

The most frequent haemodynamic complication is arterial hypertension (commonly caused by fluid overload induced by fluid therapy), immunosuppressive drugs or intense pain. Cardiac arrhythmias (mainly bradycardia) are related to imbalances of calcium, sodium, potassium and magnesium, and are mainly derived from hepatic reperfusion [2,3,15].

Respiratory complications

The main respiratory complications are pleural leakage (predominantly on the right), followed by collapsed lung, pneumo- or haemothorax. Most complications are minimal and usually managed in a conservative manner [2,3].

Table 3. Rejection Activity Index (RAI) scoring for acute cellular liver refection

Feature	Description	Score
Portal triad inflammation	Most lymphocytic inflammation involving a minority of the triads	1
	Mixed inflammatory infiltrate, containing occasional eosinophils and blasts, which affects most or all the triads	2
	Marked mixed inflammatory infiltrate, containing numerous eosinophils and blasts, which affects most or all the triads	3
Non-suppurative cholangitis	Some ducts are surrounded and infiltrated by inflammatory cells. The epithelial cells show mild reactive changes (increased nuclear/cytoplasm ratio)	1
	The inflammatory cell infiltrate affects most or all of the ducts. More than occasional ducts show epithelial degenerative changes (nuclear pleomorphism, polarity alteration, and cytoplasmic vacuolization)	2
	The inflammatory cell infiltrate and epithelial degenerative changes affect most or all of the ducts. Focal luminal disruption	3
Endotheliitis and phlebitis	Subendothelial lymphocytic infiltration involving some of the portal and/or hepatic venules	1
	Subendothelial lymphocytic infiltration involving most of the portal and/or hepatic venules	2
	As described above, with moderate or severe perivenular inflammation that extends into the perivenular parenchyma and is associated with hepatocyte necrosis	3

2. LONG-TERM CLINICAL AND THERAPEUTIC MANAGEMENT

2.1 Long-term clinical management

During the first 6 months after transplant, liver transplant recipients need to be closely managed by transplant surgeons and hepatologists. After this period, the clinical management and care of the patient is usually transferred to the patient's transplant hepatologist with close support from the primary care physician.

In this sense, it is important to determine the medical complications that the primary care clinician [18] is capable of managing and those that require the attention of the transplant centre. Generally, transplant centres manage immunosuppressive therapy, complications derived from the graft (recurrent liver diseases, infections, biliary complications), and some complications derived from immunosuppression (rejection, renal dysfunction) [19].

The primary care clinicians may help manage preventive medicine (general health maintenance), annual screenings, immunizations and some medical problems. However, most liver transplant programmes follow all the recipients in the long-term to properly adjust immunosuppressive therapy and its side effects (diabetes, hypertension, dyslipidaemia, bone diseases and pregnancy).

1) Preventive medicine

General examination of the transplant recipients is similar to that required by the general population but taking particular care of the common side effects of the transplant (hypertension, dyslipidaemia, diabetes...) [3]. In addition, immunosuppressants have numerous interactions with a wide spectrum of drugs, so patients should be asked about new medications that they are currently taking.

For patients with hypertensive problems, the patient should monitor blood pressure once a week. In patients with no hypertensive problems, a healthcare provider should monitor blood pressure every 6 months.

- **Diabetes mellitus:** Screening every 6 months.
- **Dyslipidaemia:** Annual screening (lipid profile).
- **Cardiovascular disease:** For cardiovascular risk patients conduct a stress test every 3-5 years.
- **Renal disease:** Urinalysis, microalbumin, creatinine levels and glomerular filtration every 2-3 months for the first 6 months.
- **Bone diseases:** Bone mineral density screening should be performed prior to the transplant and every year after discharge.
- **Screening for malignancies:** In particular, for carcinomas and lymphoid disorders.

2) Immunization protocol

Immunization for influenza, pneumococcal, HBA and HBV should be performed before the transplant. Generally, live virus vaccination should be avoided.

3) Other recommendations

Alcohol consumption is strictly not recommended for these patients, particularly for those with alcoholic liver disease.

2.2 Long-term immunosuppressants

The goal of long-term immunosuppression is the administration of the lowest possible immunosuppression that will prevent both significant side effects and rejection. This usually means employing an immunosuppressant as monotherapy (usually CNI) and avoiding steroids, although other strategies may be assessed (the use of MMF or T cell depleting agents); however, to date no single minimization strategy has proven superior to another [20].

Withdrawal of immunosuppression and operational tolerance are feasible in liver transplant, but the long-term clinical benefits of this strategy have not been demonstrated, and the biological mechanism that regulates immune tolerance is still unclear.

2.3 Complications

1) Late acute and chronic rejection

This complication is defined as a histologically proven, acute cellular rejection occurring more than 90 days after transplantation. In cases of severe rejection, the therapeutic procedure is the same as described for severe acute cellular rejection. In cases of moderate rejection, high doses of GC should be administered for 7 days, followed by suppression of these drugs and use of an additional agent [21].

2) Chronic rejection

Chronic rejection is defined as immune-mediated damage to the liver allograft as a result of chronic damage to the biliary epithelium and vascular endothelium, leading to potential irreversible damage to the bile ducts, arteries and veins.

This complication usually occurs at 6-12 months posttransplant, and is closely related to a failure in immunosuppressive response or as the evolution of an acute rejection [21,22]. The incidence of chronic rejection has decreased to 1.5-3% of allograft recipients thanks to the use of CNI as a long-term immunosuppressant. The clinical features are jaundice and progressive thinning, pruritus, malabsorption, severe cholestasis (>20 mg/dl) and very high levels of gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP).

Clinical features and medical records (previous acute cellular rejection episodes, primary sclerosing cholangitis, autoimmune hepatitis, HLA-incompatible) and imaging (angiography findings: rarefaction and occlusion of intrahepatic vessels) can point to this complication. But a definitive diagnosis is based on the histopathological examination of a liver needle biopsy.

For histopathological diagnosis, the main features that may be observed are dystrophic epithelial changes followed by a loss of small bile ducts, and an obliterative vasculopathy affecting large and medium-sized arteries. In accordance with these features, the chronic rejection can be classified as early or late chronic rejection (Table 4).

Neurological complications

Some patients receiving immunosuppressive regimens present neurological issues (headache and tremors), which are more frequent with tacrolimus. These symptoms usually relapse with non-selective beta-blockers, tricyclic antidepressants or calcium supplements [3].

The treatment for early chronic rejection is based on the administration of boluses of steroids (500-1,000 mg/day for 3 days) in addition to increasing the dose of the immunosuppressant and/or using an additional agent [6,22]. If the evolution is not favourable, retransplantation should be considered.

3) Late dysfunction of the graft

The prevalence of late dysfunction is progressively increasing and reaches up to 60% at 10 years post-transplant, due to disease recurrence or *de novo* hepatopathy.

4) Recurrence of the primary disease

In cases of congenital disorders, hepatic metabolic toxic liver diseases and disorders, liver transplant is curative and there is no risk of recurrence, whereas there are risks of relapse of the disease in cases of liver transplant for HCV [24], HBV, primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis, non-alcoholic and alcoholic-related hepatopathy, haemochromatosis and hepatocellular carcinoma.

The diseases that most frequently recur after liver transplantation are HCV and HBV. The use of anti-HBV immunoglobulins during and after the transplant, usually combined with tenofovir or entecavir, can prevent the recurrence of HBV. Historically, in cases of liver transplant due to HCV, there was an association with a 10% decrease in 5-year graft survival compared to HCV-negative patients. The introduction of new direct antiviral drugs before and after liver transplantation has changed this observation, and graft loss due to HCV recurrence is currently anecdotic [3].

5) Infections

Infections 1-6 months posttransplant

These are opportunistic infections secondary to immunosuppressive therapy [3,15,21,25]. The most common are:

- **CMV** is the most common pathogen during this period. Clinical signs include fever, leukopenia, thrombocytopenia and arthralgia. CMV-induced pneumonia, gastroenteritis, hepatitis or retinitis are less common. CMV infection can affect the graft and mimic a rejection.
  Histopathology lesions include mononuclear infiltration with viral inclusions and micro abscesses. The presence of ductopenia is uncommon. Other viruses, for instance VZV, EBV, respiratory syncytial virus (RSV), hepatitis-6 virus, influenza and adenovirus can also affect patients during this period. In particular, EBV is closely related to posttransplant lymphoproliferative disorders (LPD).
- ***Aspergillus spp.*** are responsible for 15-20% of posttransplant fungal infections. They usually induce pneumonia but can even affect the central nervous system.
- **Other opportunistic pathogens** such as *Nocardia, Listeria, Cryptococcus, Mycobacterium tuberculosis* (M. tb) can also have an effect during this period. Although M. tb infection is more related to reactivation of the infection than *de novo* infection, it is closely related to immunosuppression therapy, and leads to a spreading of the infection with high morbidity and mortality rates.

Infections later than 6 months after liver transplantation

The risk of infection decreases after 6 months due to lower doses of immunosuppressive agents, and recipients are progressively considered an immunocompetent population (except in patients who still require a high dose of immunosuppressants) [3]. The risk of opportunistic infections still remains high for transplant patients, and they are susceptible to community-acquired infections, i.e., *Legionella Spp*.

6) Chronic kidney disease

Chronic kidney disease (CKD) is a known common complication after liver transplantation which affects a high proportion of transplant patients (70-80%) and has a major impact on graft survival [26,27]. The incidence of stage 5 CKD (estimated GFR <15 ml/min) is approximately 25% 10 years after transplantation.

There are several factors which may induce CKD. The major one t is pretransplant renal dysfunction, but other factors include pretransplant and posttransplant kidney injury, diabetes mellitus, hypertension, HCV and renal dysfunction induced by CNI immunosuppressants, which are the main cause of end-stage renal disease after transplantation due to their renal vasoconstriction and profibrogenic properties [27].

The treatment of CKD is based on minimization of CNI dosage for these patients or replacing CNI with other non-nephrotoxic immunosuppressive agents, for example MMF or mTOR inhibitors, control of hypertension, dyslipidaemia and diabetes. The renal function 80% of CKD patients can stabilize or improve. If the CKD progresses to end-stage renal disease, the therapeutic option is a kidney transplant.

7) *De novo* malignancies

Impairment of immunosurveillance leads to the uncontrolled proliferation and malignant transformation of cells. In this context, a long-term induced state of immunosuppression and the aging of transplant recipients increases the risk of developing such neoplasms [29,30].

Among liver transplant recipients, this incidence ranges from 3% to 16%, which is significantly higher than in the general population. This range that will probably increase due to improvements in the overall survival of transplant recipients. This complication is a major cause of late death for transplant recipients, up to 25% of patients at 3 years posttransplant [31].

Kaposi's sarcoma and LPD can develop in the short-term, while skin carcinomas, cervix cancer and anogenital carcinomas are long-term neoplasms. Skin tumours are the most frequent, with an incidence of 1.6-22% (20-50 times higher than in general population). The prevalence of basal cell epithelioma and squamous cell carcinoma represent 90% of these neoplasias.

Lymphoproliferative disorders are the second most common malignancy among adult liver transplant recipients (30-times higher than in the general population). Over 90% of the cases are non-Hodgkin lymphoma related with EBV infection. Kaposi's sarcoma has an incidence of 0.2-3% among transplant recipients (100 times higher than in the general population). Several reports have suggested that human herpesvirus-8 infection is closely related to the development of this neoplasm in these patients.

8) Other long-term medical complications

- **Hypertension:** An ideal blood pressure of 130/80 mmHg is reasonable for liver transplant recipients. Between 65-70% of liver transplant recipients develop hypertension after transplantation, and although the cause of this complication is multifactorial, it is usually related to the administration of corticosteroids and CNI. The treatment initiates with CNI dose modulation (if serum levels are high) or, if medication is required, non-selective beta-blockers, ACE inhibitors or ARB may be used. The use of diuretics is not recommended as a primary therapy due to their potential to exacerbate hydroelectrolytic disorders [31].
- **Diabetes:** Weight gain, steroids, CNI or even HCV predispose to the development of this complication. The incidence of *de novo* diabetes in transplant recipients ranges from 5-30%, does not affect overall survival during the first year but is related to decreased survival at 10 years. Screening for glucose levels and haemoglobin AC1 is recommended every six months. Treatment is based on nutritional therapy with weight loss and standard medication (use of insulin for the first 6 months after transplant and early steroid tapering) [33-35].

» **Obesity:** Approximately one third of posttransplant recipients will become obese after transplantation, mainly caused by a sedentary lifestyle, increased intake and therapy with immunosuppressants (mainly corticosteroids). Calorie-restrictive diets, increased physical exercise and tapering of corticosteroid are usually the most common therapeutic options to treat this complication.

» **Dyslipidaemia:** Hypercholesterolemia in liver transplant recipients seems to be induced by corticosteroids and CNI administration. Early corticosteroid withdrawal and lowering the maintenance dose of CNI usually improves cholesterol levels [18,32,34].

» **Metabolic syndrome:** This disease is the combination of hypertension, diabetes, dyslipidaemia and obesity. As immunosuppressants can exacerbate these symptoms, an evaluation of these medical problems should be performed before transplantation. Since this syndrome is closely related to increased morbidity and mortality rates in liver transplantation, its early detection and treatment are essential.

» **Cardiovascular disease:** Closely related to hypertension, diabetes, obesity and dyslipidaemia, this disease has an increased risk of cardiovascular death. The prevention and treatment of all the described complications are priorities for these patients [19,32].

» **Metabolic bone diseases:** Approximately 20-40% of recipients suffer bone loss or fractures within the first 6 months following transplantation due to osteopenia induced by the use of steroids or secondary to several liver diseases (primary biliary cirrhosis) [3]. The use of calcium supplements, vitamin D and bisphosphonates may prevent these diseases.

Table 4. Histopathological features of early and late chronic rejection

Structure	Early CR	Late CR
Bile duct	Bile duct loss <50% of portal triads. Many ducts show degenerative changes, partially lined by epithelial cells	Loss of >50% in portal triads. Degenerative changes of the remaining bile ducts
Perihilar bile ducts	Inflammatory degenerative changes, focal foam cell infiltration	Mural fibrosis
Portal triad arterioles	Occasional loss, which affects <25% of portal triads	The loss affects >25% of portal triads
Perihilar hepatic artery branches	Inflammation of the intima, focal foam cell infiltration	The lumen is surrounded by subintimal foam cells. Fibrointimal proliferation
Central vein and zone 3 hepatocytes	Inflammatory infiltrate which affects to the intima and lumen. Necrosis and inflammation of zone 3 hepatocytes. Mild perivenular fibrosis	Focal obliteration. Presence of inflammatory infiltrate. Severe fibrosis

CONCLUSIONS

The aim of the immediate postoperative follow-up is to maintain haemodynamic function in the patient and start immunosuppression in order to avoid rejection.

The most common complications which appear after transplant are related to the surgical procedure and function of the graft.

Immunosuppressive therapy should be managed by a transplant surgeon or haematologist in order to avoid complications. Infections are the most frequent complications related to immunosuppressive therapy.

Long-term follow up can be managed by a primary care clinician, however, issues related to immunosuppression and the biliary tract are managed by the transplant surgeon or hepatologists.

The most common long-term complications are related to immunosuppression therapy. Infection is the leading cause of mortality following liver transplantation, so patients who develop fever or other signs of infection require urgent evaluation.

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TOPIC 4 - Unit 1

Pancreas transplant: indications and waiting list

ORGAN TRANSPLANTATION

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INTRODUCTION

The main objective of this unit is to identify the indications for pancreas transplantation, discuss the different modalities and consider their advantages and disadvantages. In the case of simultaneous pancreas and kidney transplantation, the unit explores different indications according to parameters such as age, type of diabetes, and the recipient's degree of kidney failure.

We describe the pretransplant workup for potential candidates, the main objective of which is to identify surgical risks, guarantee that no exclusion criteria exist, and document the extent of the secondary complications of diabetes. This pretransplant workup enables us to identify pathologies which may contraindicate the transplant or preclude treatments which may be necessary before transplantation (i.e., cardiac revascularization).

Finally, we endeavour to establish guidelines for a series of controls to follow while patients are on the waiting list. This is essential to detect any newly arising conditions or detect worsening of existing disease that might contraindicate transplant.

1. INDICATIONS FOR EACH TRANSPLANT MODALITY

The last 20 years have seen an increase in the variety of options for diabetes treatment ranging from oral anti-diabetic agents, which exert their action at different points of the glucose metabolism, to different formulations of insulin. These include short *vs.* long-acting, mixed formulations, insulin pumps with the capacity to predict hypoglycaemias and suspend insulin perfusion in advance, or dual formulations of insulin combined with glucagon connected to a mobile device that enable the patient to "inform" the insulin pump about the type of meal they are about to eat. Despite all these advances, more than 50% of diabetic patients fail to achieve an HbA1C <7.0%.

When performing a pancreas transplantation, the main objective is to transplant an amount of β-cell mass which will enable the recipient to achieve euglycaemia without the support of any other anti-diabetic treatment.

Allograft transplantation requires an open surgery and has only been possible since the introduction of immunosuppressive therapy. Transplantation poses several risks for recipients, such as anaesthetic and surgical complications, as well as short- and long-term complications from immunosuppression, such as infections, cardiovascular disease, or cancer.

Pancreas transplantation is therefore only indicated for patients with insulin-dependent diabetes mellitus (IDDM). Selection criteria are based on a positive benefit/risk balance as well as the reality of organ shortage.

Table 1 shows the general indications alongside the absolute and relative contraindications for a pancreas transplant. Nevertheless, each transplant modality has its own particularities which will be detailed later.

Table 1. Indications and contraindications for pancreas transplant

Indications
SPK: Diabetes mellitus and terminal or preterminal kidney failure
PAK: Diabetes mellitus and functional prior kidney transplant (live or deceased donor)
PTA: Diabetes mellitus type 1 without kidney disease but with undetected life-threatening severe hypoglycaemia, or metabolic complications requiring frequent hospitalizations. There must be evidence of the failure of other alternatives like insulin pumps and continuous glycaemia control.
Absolute contraindications
Severe non-revascularizable coronary disease
Severe ventricular dysfunction
Chronic advanced lung or liver disease
Active infection
Active neoplasm or without appropriate remission period (cutaneous epitheliomas excluded)
Serious psychological or psychiatric disorders
Drug or alcohol abuse

Extreme obesity
Relative contraindications
Age <18 or >55 years old
Obesity (BMI <30 kg/m^2)
Recent acute myocardial infarction
Active digestive haemorrhage
Recent retinal haemorrhage
Cerebrovascular or symptomatic peripheral vascular disease
Severe autonomic neuropathy
Severe diabetic gastropathy
Active smoker

1.1 Simultaneous pancreas and kidney transplant (SPK)

This is the most common pancreas transplant modality and has the best results. Indications essentially include patients with IDDM and stage 4-5 chronic kidney disease (glomerular filtration rate >30 mL/min or dialysis). Kidney disease is most often secondary to diabetic nephropathy. Parameters to consider before inclusion on the waiting list are age, DM type and extent of diabetic complications.

Age

Age is not an absolute contraindication, and candidates up to the age of 50 are generally accepted. Individual evaluation is usually performed for potential candidates between the ages of 50 and 55. Nevertheless, as previously stated, improvements in insulin treatment have led to a better control of diabetes at early stages, with secondary complications, such as diabetic nephropathy, presenting later. Therefore, the age for acceptance is likely to increase in the next decade.

Diabetes type

Pancreas transplant is essentially indicated in type 1diabetes (DM). This type of patient is usually young, with a history of diabetes >15 years, and without any endogenous insulin production due to β-cell loss secondary to an autoimmune process. Posttransplant disease recurrence is rare.

Selected patients with maturity-onset diabetes of the young (MODY) and type 2 DM (age <50 years, BMI <30 kg/m^2, under insulin treatment >5 years, requiring insulin dose <75 U/day, with peptide C levels <5 ng/mL) could also benefit from pancreas transplantation.

However, according to data received from the latest US Pancreas Transplant Register (OPTN/SRTR), type 2 DM only represents 8% of all transplants performed in recent years. Despite the short-term results being satisfactory and comparable to those of type 1DM, they are slightly lower in the long term; therefore, greater experience is required to assess the benefits of transplant for this group in the future.

State of diabetic complications

Another parameter to consider when evaluating a patient for a transplant is the presence and severity of diabetic complications. The condition that can influence this decision the most is severe vasculopathy. Although the contraindications for SPK or kidney transplant alone may occasionally be the same in terms of cardiovascular disease, the implantation of two organs requires a more aggressive surgery, longer anaesthesia, and a higher probability of presenting some kind of surgical complication or the need for reintervention.

Furthermore, the presence of severe calcifications in the iliac vessels, where vascular anastomoses of organs are usually performed, in addition to the existence of severe peripheral vasculopathy, may negatively influence technical aspects of graft implantation. In such cases, priority is always given to the kidney transplant.

Although other microvascular complications of diabetes such as retinopathy or neuropathy are almost always present, they rarely represent a transplant contraindication in themselves, i.e., they should be assessed as part of the patient's general condition.

1.2 Pancreas after kidney (PAK)

Indications

The decision to perform a pancreas transplant in patients with a previously successful kidney transplantation (PAK) can result from different scenarios:

a) A candidate for simultaneous pancreas and kidney transplant (SPK) with a suitable living donor receives a live kidney transplant as soon as possible and is subsequently kept on the waiting list for a pancreas transplant alone.

b) A candidate for SPK has the possibility of receiving a deceased donor kidney transplant before SPK (i.e., from centres with short waiting lists for kidney transplant).

c) A candidate who has previously lost a pancreas allograft, waits for a pancreas re-transplant while maintaining a functioning kidney graft from the previous donor.

Pancreas outcomes for PAK are significantly worse than those of SPK. Moreover, PAK implies the transplantation of organs in two different surgeries. Nevertheless, being able to receive a kidney transplant from a living donor offers the patient the possibility of a preemptive transplant (i.e., before the need for dialysis) or shortly after starting dialysis.

Patient survival is better for SPK in comparison to living donor kidney transplant alone in type 1 DM. Therefore, a pancreas transplant poses an additional survival benefit for these patients.

When proposing a patient for a PAK (live donor kidney), the most important decision factor should be the expected time on waiting list for SPK. For patients with a suitable living donor and the possibility of receiving a preemptive transplant, PAK can be a suitable option since it may avoid the need for dialysis. Clinical trials have not established a clear cutoff between the patient and/or graft survival benefits of PAK *vs.* remaining on the waiting list for an SPK; however, it is generally accepted that candidates with an expected time on the waiting list >2 years before receiving an SPK should be offered the possibility of PAK.

Organ shortage

This subject has acquired greater interest in recent years due to the current shortage of young, deceased organ donors and the resulting increase in time on the kidney-pancreas waiting list. In some centres, such as Minneapolis, PAK represents up to 50% of pancreas transplants, the majority having previously received a live donor kidney transplant. Table 2 shows the main advantages and disadvantages of SPK. In addition to the advantages presented, PAK from a living donor increases the global organ donor pool, by increasing the number of organs available for recipients of deceased kidney pancreas donation.

Table 2. Pancreas transplant after living-donor kidney transplant

Advantages
Minimizes or eliminates need for dialysis. Avoids morbidity and associated cost
Shorter more straightforward surgery
Non-uremic receiver and better general condition
Disadvantages
Patient requires 2 surgeries and anaesthesia
Requires 2 rounds of immunosuppression induction
Greater incidence of acute rejection with more graft losses due to immunological reasons
Long-term pancreas survival lower than for SPK

Timing

Indications with regard to recipient's age, DM type and vascular state are the same as for SPK. However, it is essential the recipient's previously transplanted kidney has stable function. Increasing immunosuppression doses with nephrotoxic effects, such as calcineurin inhibitors, could worsen graft function or even trigger premature loss if the patient already suffers the chronic impact of medication. For this reason, transplant is advised in patients with a creatinine clearance equal to or over 40 mL/min.

One of the questions posed in this modality of transplant is when to perform a pancreas transplant after a kidney transplant. There is no established time limit, and it depends on the evolution of each patient after their kidney transplant. Although there seems to be improved pancreatic graft survival when the interval between both is under 12 months, and some authors even believe the optimum interval between both transplants is under 4 months.

1.3 Pancreas transplant alone (PTA)

For diabetics without kidney failure with few or no other secondary complications, PKA would seem the ideal transplant. This recipient group is the one that could benefit from early positive effects in preventing the onset of secondary diabetic complications thanks to early metabolic control. However, the risks of the intervention and the immunosuppression to which the patient would be exposed for life do not always justify the hypothetical advantages of the transplant. Indeed, pancreas or islet transplantation is currently proposed as the 4th line of therapy for patients with type 1 DM (Figure 1).

Outcomes for PTA are slightly lower than those for PAK and SPK and the incidence of technical complications (essentially graft thrombosis) is slightly higher than for the other transplant modalities. Likewise acute rejection is also higher; therefore, indications continue to be much stricter.

Current indications for PTA are:

1. Type 1 DM >10 years disease history.
2. Age between 20-55 years.
3. Glomerular filtration rate >60 mL/min and proteinuria <2 g/day.
4. Brittle diabetes:

a. >3 episodes of diabetic ketoacidosis or hypoglycaemia/year.

b. Persistence of symptoms for 6 months, following treatment with a sensor-augmented insulin pump (SAP) with low-glucose suspend (LGS).

c. Confirmation of glucose instability during a week of hospital admission.

d. Severe compromise of daily personal and work activities.

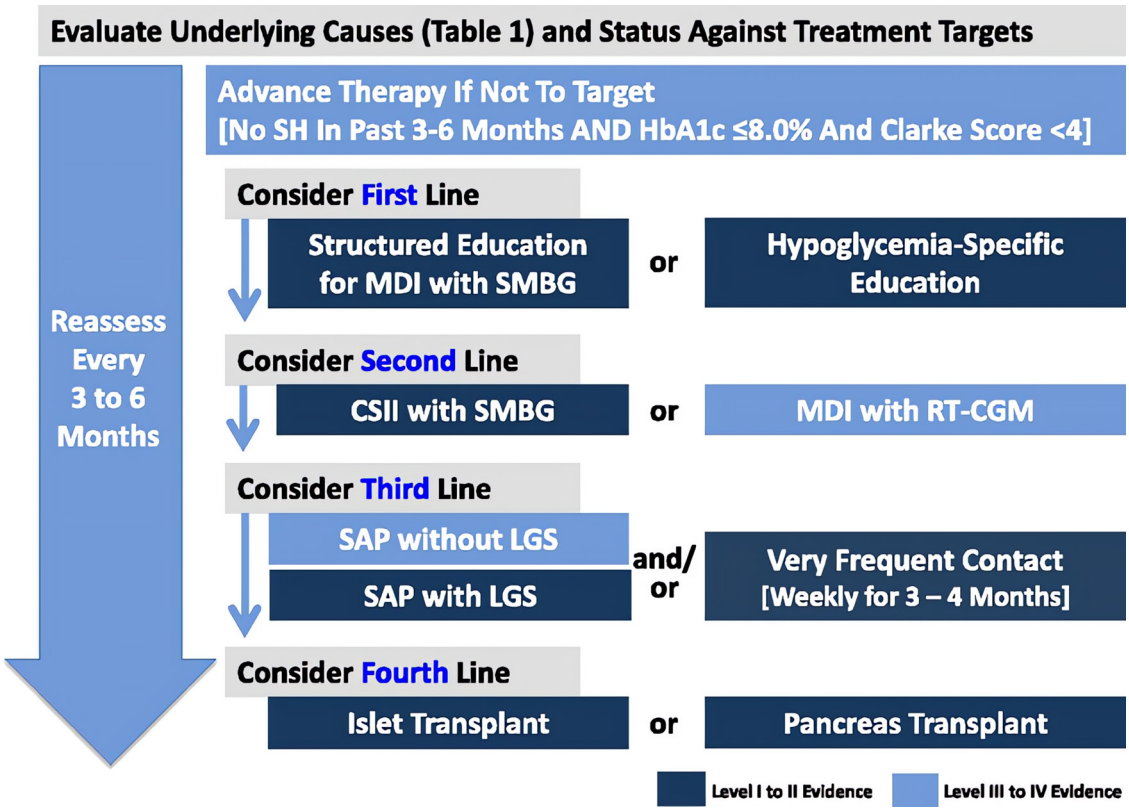

Figure 1. Proposed treatment algorithm for patients with T1DM and problematic hypoglycaemia.

2. CANDIDATE STUDY AND EVALUATION

When evaluating the potential pancreas transplant candidate, on the one hand, we need to consider the extreme shortage of suitable pancreas grafts, and on the other, the long-term medical outcome of the impact of diabetes. This makes it necessary to perform a standardized, thorough evaluation of each candidate.

Transplant candidate evaluation enables detection of the best candidate and who would most benefit. Whenever possible, patients should be evaluated as soon as chronic kidney disease progresses to stage 4. This may enable an early transplant, therefore reducing the progression of the micro- and macrovascular complications of diabetes, as well as lessening the cardiovascular risk associated with dialysis.

Patient evaluation for pancreas transplantation follows some of the general principles which are transversal to all solid organ transplantation, such as the ability to withstand the surgical procedure, exclusion due to an active infection or an untreated neoplasm, the ability to understand the implications of the procedure, and comply with posttransplant treatment and outpatient visits. (Table 3) present a summary of the workup needed for every patient before transplantation.

Table 3. Study of recipient for pancreas transplant

Analysis
Blood type and HLA typing
CDC-PRA and solid phase (Luminex®)
Complete haemogram
Glycaemia, HBA1c, C peptide, anti-GAD
BUN, creatinine, creatinine clearance test, proteinuria, electrolytes
Ca, P, FA y PTH
GOT, GPT, GGT, bilirubin
Lipoprotein electrophoresis
Clotting tests
Thrombophilia study (if history of thrombosis)
Viral serologies (HBV, HCV, HIV, EBV, CMV). Sero-agglutination and luetic serology.
Radiology
Anteroposterior thoracic X-ray
Upper GI series (optional)
Angio-CAT (to visualize iliac vessels and celiac trunk)
Voiding cystourethrogram in the event of prolonged anuria, urinary pathology or use of urinary derivation technique to drain pancreatic exocrine secretion.
Other examinations
PPD
Abdominal ultrasound
Functional respiratory tests
Echocardiogram and myocardial perfusion scan (persantine MIBI)
Coronary angiography (if appropriate)
Lower limb and/or carotid (if appropriate) Doppler
Fundus
EMG and VCN
Gynaecological/urological examination
Transplant team evaluation (surgeons, endocrinologist, nephrologist, anaesthetist)

Since candidates for a pancreas transplant are patients with longstanding diabetes, a thorough evaluation of cardiovascular disease must be conducted. Focus on other complications of diabetes, such as microvascular complications, retinopathy and neuropathy should also be addressed, since they may present as complications for patient compliance, or lead to frequent hospital admissions in the post-transplant period. An immunological evaluation must also be performed before transplantation, including auto- and alloimmune testing, to identify patients at risk of graft rejection or disease relapse. The following section discusses the particularities of assessment before inclusion on the waiting list.

Hormonal evaluation and immunological workup

Posttransplant euglycaemia without the need for antidiabetic drugs (oral or insulin) is most successful in patients with diabetes due to insufficient endogenous insulin secretion. C-peptide is a short, 31-amino-acid polypeptide secreted with insulin as proinsulin. Since it is secreted in equimolar amounts to insulin, determination of C-peptide plasma levels in morning fasting condition is usually sufficient to identify patients with insulin deficiency. Low or undetectable levels indicate an absence of insulin secretion. When positive (>5 ng/mL), it contraindicates pancreas transplant, since a peripheral resistance to insulin is the most probable cause of impaired glucose metabolism, and such patients should be evaluated by an endocrinologist for adjustment of antidiabetic therapy.

An immunological workup is also performed prior to transplantation, aimed at two different settings. Since type 1 DM is an autoimmune disease, determination of autoantibodies against β-cell are usually performed. Several autoantibodies can be measured from serum samples, including insulin autoantibodies, autoantibodies targeting the phosphatase-related IA-2 molecule, antibodies targeting glutamic acid decarboxylase (GAD), and zinc-transporter autoantibodies (ZnT8) Even though the whole panel can be performed, measurement of antibodies against glutamic acid decarboxylase (anti-GAD) is usually sufficient before transplantation. These are usually negative prior to transplantation due to longstanding type 1 DM, with a consequent absence of antigen (viable β cells) stimulation, however positive values are not a contraindication for the intervention. Posttransplant reappearance may preclude a diabetic relapse. In this context, the reappearance of more than one antibody (anti-insulin, anti-IA2, anti-GAD, or anti-ZnT8) has a higher predictive value for disease relapse than an increase in the levels of a single one.

Anti-HLA antibodies are also screened prior to transplantation. Rejection in allotransplantation occurs mainly through major histocompatibility complex (MHC) recognition by the recipient's immune system. Recipient human leukocyte antigen (HLA) can be determined pretransplant. Also, a recipient may develop non-self HLA antibodies before transplantation during sensitization events (pregnancy, blood transfusions, and previous transplants). Screening is usually performed by mixing recipient serum with a pool of cells representative of the HLA from possible donors of a determined geographic region. In a reaction of complement-dependent cytotoxicity (CDC), in the presence of cell lysis following the addition of recipient serum, it is assumed the former has pre-formed antibodies against the HLA of that cell. The total amount of anti-HLA antibodies against a representative donor pool sample is known as panel-reactive antibodies (PRA). Additionally, engineered lab-based techniques allow determination of antibodies against a pool of beads. Known as solid-phase assays, Luminex® screening is more sensitive than CDC, but less specific. Both CDC and Luminex® are performed to determine immunological risk prior to transplantation.

Retinopathy and polyneuropathy due to DM

Retinopathy is a microvascular complication of diabetes and is present in >85% of patients with type 1 DM at the onset of nephropathy (Figure 2). It is, therefore, present to a greater or lesser extent in all transplant candidates. Even though it is not considered an exclusion criterion for transplant, a pretransplant evaluation by an ophthalmologist is advisable since therapy with corticosteroids may worsen associated diseases such as cataracts or glaucoma.

As with retinopathy, diabetic neuropathy will also be present in most patients. This is also often worsened by kidney failure, but it rarely contraindicates a transplant.

Nevertheless, severe dysfunction of the autonomous nervous system should be taken into account, because of the negative incidence it may have on the patient survival.

Furthermore, diabetic neuropathy may often affect the bladder, leading to incontinence or difficulty urinating. If urinary derivation is used as a surgical technique to drain pancreatic exocrine secretion, a voiding cystourethrography is advised to rule out pathology at the bladder neck, bladder and urethra level, in addition to cystomanometry to study bladder function and evaluate the degree of neuropathy involvement.

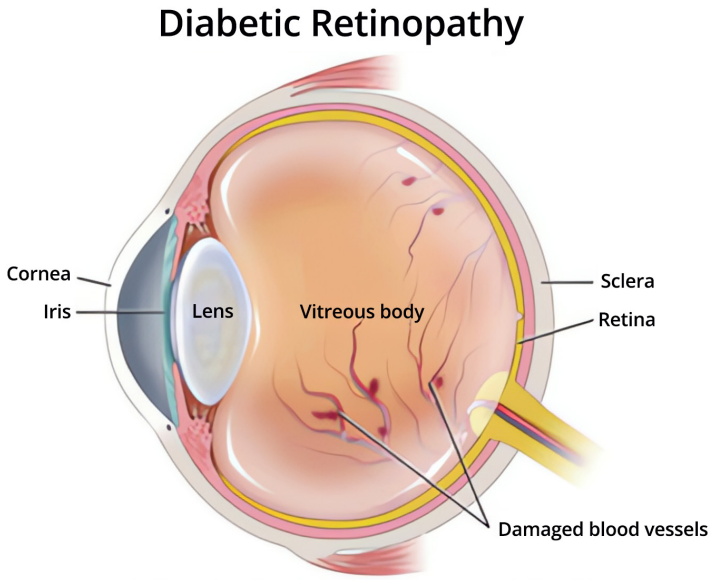

Figure 2. Diabetic retinopathy.

Vasculopathy

This is the most serious complication and should be thoroughly evaluated before inclusion on the waiting list due to the implications it may have for posttransplant mortality and morbidity.

The great incidence of cardiac arteriosclerosis in diabetics is well known, and they may sometimes present ischaemic lesions, or a heart attack without chest pain or other heart symptoms. To identify coronary risk in asymptomatic patients with a normal ECG, a pharmacological persantine MIBI stress test is advised. Should the test indicate a condition, a coronary angiography is performed to identify existing lesions with greater accuracy and apply appropriate treatment before a transplant. The presentation of a prior history of myocardial infarction, angioplasty or coronary bypass should not necessarily be contraindication for transplant unless the infarction was recent, the coronary angiography finds significant lesions that are not susceptible to correction, or there is severe ventricular dysfunction.

Likewise, considering the vascular anastomoses that will be performed during the intervention, a CT angiography should be performed to rule out lesions, essentially at iliac vessel and celiac trunk level, which might hinder graft implantation.

Team evaluation policy

On completion of the study of a prospective candidate and before their inclusion on the waiting list, the combined evaluation of the entire transplant team (nephrologist, endocrinologist, anaesthetist and surgeons) is advisable.

This provides not only a forum for analysis of the potential risks and benefits of the transplant in each case but can also give the patient with more detailed information.

3. WAITING LIST INCLUSION CRITERIA AND PERMANENCE

Before inclusion on the pancreas transplant waiting list, there are several points that must be verified:

- The patient meets the requirements established in the indications.
- They have undergone the corresponding studies and assessment by the surgical team.
- They have been clearly and comprehensibly informed of the advantages and possible complications of the transplant.
- The patient freely chooses this form of treatment.

Practical arrangements

It is also advisable to inform the patient that their possible donor may be detected at any time, on any day. The patient should, therefore, know in advance how to reach the transplant centre when the alarm triggers, and approximately how much time they have to do so.

At the time of notification, the patient should report any incident of interest which might have occurred since the last control.

Transplant procedure

Furthermore, it is advisable that both the patient and their immediate next of kin are informed in advance of the approximate duration of the intervention, the ICU stay during the first hours after surgery, the approximate duration of hospital admission after transplant, and the immunosuppressive treatment to be given.

Having all this information beforehand gives both the patient and their next of kin better knowledge of the transplant process, which is beneficial in terms of expectations related to duration of the hospitalization period.

Waiting list management

It is essential that the patient should be aware of the importance of maintaining regular contact with the transplant centre during their time on the waiting list. The high incidence of complications these diabetics may present, particularly those who have chronic kidney failure and are also awaiting simultaneous kidney transplant, requires strict control and follow-up before transplantation. Ideally, the patient should receive a visit from a member of the transplant team or collaborating doctor every 3 to 4 months. Only in this way is it possible to detect events which may represent a temporary contraindication for the intervention.

Thus, the onset or worsening of any pathology such as intermittent claudication, precordial pain, ischaemic lesions or ulcers on feet, would require undertaking new studies before performing a transplant, with temporary or even permanent exclusion from the waiting list.

CONCLUSIONS

- There are different modalities of pancreas transplants in IDDM patients. The most frequent is SPK, which is indicated in patients who have chronic kidney disease. PAK is indicated in patients with a transplanted kidney from live or deceased donor, or for pancreas re-transplants. PTA is indicated for patients with labile diabetes requiring frequent hospitalizations and/or severe hypoglycaemic episodes but without kidney failure.
- The best pancreas transplant patients are those with type 1 DM, under the age of 50, although patients with type 2 DM may also be considered, as may patients between 50 and 60. The state of complications secondary to diabetes should also be evaluated before indicating a transplant, with particular focus on cardiovascular disease due to its potential influence on the transplanted patient's morbidity and mortality.
- The patient should be well-informed regarding transplant options, so they can freely choose the option which best suits their needs. Likewise, information should be provided about possible complications related to surgery, postoperative complications and/or longer-term problems related to immunosuppression. Once included on the waiting list, the patient should maintain periodical contact with the transplant centre for detection of the onset of any pathology that requires treatment before transplant or may be a contraindication.

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TOPIC 4 - Unit 2

Organ evaluation and surgical procedure (techniques and surgical complications)

ORGAN TRANSPLANTATION

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INTRODUCTION

William Kelly and Richard Lillehei performed the world's first clinical pancreas transplant at Minnesota University on 17 December 1961. However, it was not until the introduction of calcineurin inhibitors (cyclosporine in 1980 and tacrolimus in 1990) when pancreas transplantation became a viable, valid treatment option for insulin-dependent type I diabetic patients.

Improvements in immunosuppressive therapy together with a drop in postoperative complications thanks to developments in surgical techniques have resulted in the better patient and graft survival of recent decades.

Correct donor viability criteria for pancreas extraction, together with standardized surgical techniques and strict organ recipient selection criteria should result in the favourable outcome of a pancreas transplantation.

This unit addresses all of these factors.

1. ORGAN EVALUATION CRITERIA

Pancreas donor availability

Correct donor selection criteria are crucial in pancreas transplantation, and in most cases the pancreatic graft comes from a deceased donor.

In many centres, there is a discrepancy between the number of recipients on the waiting list and the number of available donors that fulfil the acceptance criteria for pancreas transplantation.

According to the OPTN/SRTR 2012 register on annual pancreas transplant data recently published by Israni AK et al. [3], the number of pancreatic donors has declined since 2005 in combination with a low donation rate. Despite this alarming scenario, the proportion of "optimal" donors (18-30 years old) has increased in comparison to >50 years-old donors.

In an attempt to reduce the waiting list and improve results, different alternatives have been established, which include pancreas transplants with grafts taken from donation after cardiac death (DCD) that have shown promising results [4]. Furthermore, at the time of writing, over 160 segmental and islet pancreas transplants from live donors have been performed worldwide since 1977 [5]. Although it should be noted that the latter involves an increased risk for the donor of developing diabetes compared to general population.

Donor organ suitability

The suitability of a deceased donor pancreas is based on both general acceptance criteria and specific pancreas acceptance criteria. In demographic terms, the ideal donor is a donor after brain death (DBD) between 10 and 40 years of age, with a minimum weight of 30 kg, a BMI under 27.5 kg/m^2 and cause of death other than cerebrovascular disease [6].

The 2005 consensus meeting of the Spanish National Transplant Organization [7,8] in Madrid defined the following requirements for donors:

- without acute transmittable infectious diseases;
- no malignant diseases;
- no history of diabetes or alcoholism;
- an absence of cardiovascular conditions or pancreatic trauma.

Macroscopic evaluation is a major determinant for organ acceptance. The presence of pancreatic oedema or pancreatitis at the time of extraction that does not remit after the administration of albumin or mannitol, or abundant peripancreatic are frequent reasons for excluding a donation.

Documented pancreatic hypoperfusion episodes prior to donation, such as hypotension or cardiac arrest, or a prolonged ICU stay, should be evaluated individually, based on laboratory tests and macroscopic appearance. Cold ischaemia time (CIT) should not exceed 16 hours (this may vary according to group), with an ideal CIT cutoff being <12hours.

2. SURGICAL TECHNIQUE FOR DONOR. EXTRACTION AND PRESERVATION

The extraction technique is well-documented [9,11], whether intended for a recipient enteric or vesical derivation approach. It is necessary to extract the entire pancreas together with a duodenal segment, the vascularization of which is dependent on the anatomy of the coeliac trunk, superior mesenteric artery (SMA) and portal vein (Figure 1).

As this vascularization is shared with the liver, surgical techniques have been developed enabling joint extraction of both organs, with either *in situ* or bench table split. In specific cases of haemodynamic instability, extraction must be quick or performed as a block, enabling perfusion as rapidly as possible.

Surgery starts with a xiphopubic incision, including sternotomy and pericardial aperture. The first step consists of a thorough examination of all organs to identify any potential macroscopic evidence for contraindications to donation. Immediate vascular exploration is important to ensure rapid cannulation in the event of instability.

Dissection and exploration are performed of the abdominal aorta ligatures over the bifurcation and infrarenal cava, and of the lower mesenteric vein in the event of portal cannulation via this vein. This varies according to surgical team (Figure 2).

Next, the SMA is dissected, above and to the left of the left renal vein, with the vena cava confluence and a vessel-loop passed around it. After opening the minor sac, sectioning the gastro colic ligament to expose the entire anterior surface of pancreas body and tail an initial organ evaluation is performed as is palpation of the pancreatic head.

The next stage consists of dissecting the hepatic hilum to identify possible anatomical variations of the hepatic artery which might influence the type of procedure to be used. The most common are the right hepatic artery from the SMA and left hepatic artery from the gastric coronary artery. The choledochus is dissected and sectioned in the most distal part. An incision is made in the gallbladder at fundus level and lavage of both bile duct and gallbladder is with physiological serum.

The gastroduodenal artery is identified and the hepatic artery itself dissected to the coeliac trunk. Furthermore, the left gastric artery and coronary vein are identified, as are the lymphatic vessels on the top border of the pancreas. The splenic artery is individualized and marked with Prolene 6/0 suture to impede its retraction into the pancreas.

A silk ligature must pass through the abdominal aorta over the coeliac trunk after blunt dissection of the oesophageal hiatus. Finally, after identifying the gastric coronary vein, the portal vein is dissected. It is important to perform the Kocher manoeuvre to access the whole duodenum and posterior face of the pancreas, which should be performed using the "non-touch technique". To release the lower pancreatic face, the entire transverse colon is moved to the splenic angle. Subsequently, all the ligaments securing the spleen to the retroperitoneum are separated from the kidney and left adrenal gland, likewise those securing the body and tail to the retroperitoneum.

Likewise, complete the section of short gastrosplenic vessels and dissection of the duodenum below the pylorus and at fourth portion level section for subsequent sectioning at these two levels by means of an auto-suture device.

Once dissection is complete at intrathoracic and abdominal level, and before the **cannulation stage**, intravenous sodium heparin is administered (3 mg/kg). Next, the aorta is cannulated above the bifurcation next to the portal system cannulation (via the superior or inferior mesenteric or portal vein) and the supracoeliac aorta is clamped to begin preservation solution perfusion.

Next, the vena cava is drained after opening it at an intrathoracic level or through a drainage cannula placed in the inferior vena cava. Then crushed ice is placed over the organs to maintain them at the right

temperature. On completion of perfusion, the pancreas and liver are separated *in situ*. It is generally accepted that the coeliac trunk must accompany the liver. The splenic artery is divided just below its commencement at the coeliac trunk.

The aorta at SMA level is laterally sectioned to visualize the renal arteries. The SMA should be ligated just after the origin of the inferior pancreatic duodenal artery. In short, the aortic patch is divided into two, the hepatic with the coeliac trunk and the pancreatic with the SMA. The intrahepatic vena cava is sectioned above the junction of the renal veins. The suprahepatic vena cava is divided with the surrounding diaphragm.

Lastly, the portal vein is divided halfway between the liver and pancreas. Finally, the pancreas is extracted on completion of liver extraction. Instead of *in situ* separation, some authors perform the extraction en bloc and later separate both organs on the bench.

Next, the iliac vessels (arteries/common iliac veins and their bifurcations) are extracted and distributed between the pancreatic and hepatic grafts to re-vascularize the liver and/or pancreas.

The organ is packed into a sterile bag with a preservation solution at 4ºC. This bag is protected by introducing it into another two bags, and transported to the hospital where the recipient awaits. Bench surgery can be done at the extraction hospital or prior to transplantation in the recipient hospital.

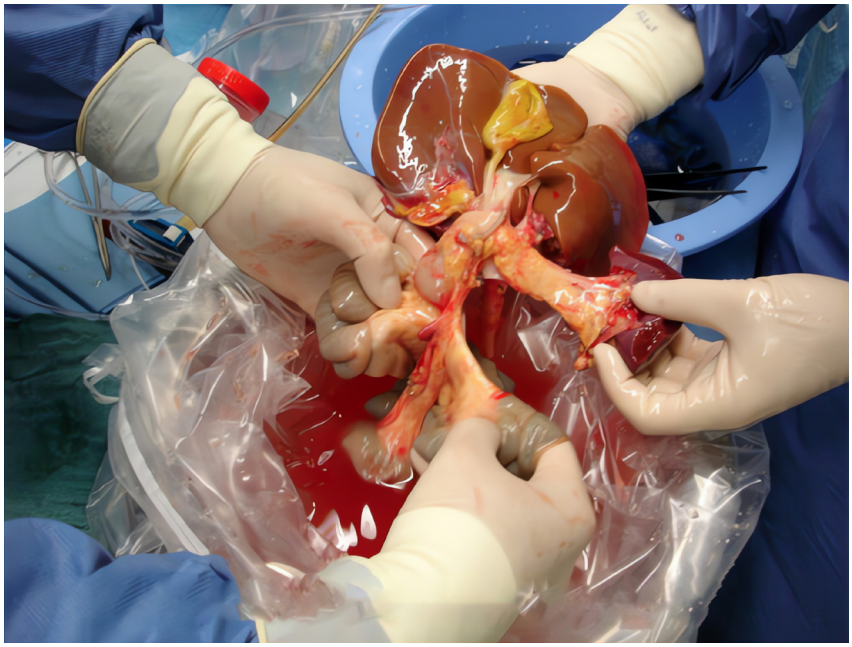

Figure 1. En bloc liver, pancreas, intestinal graft.

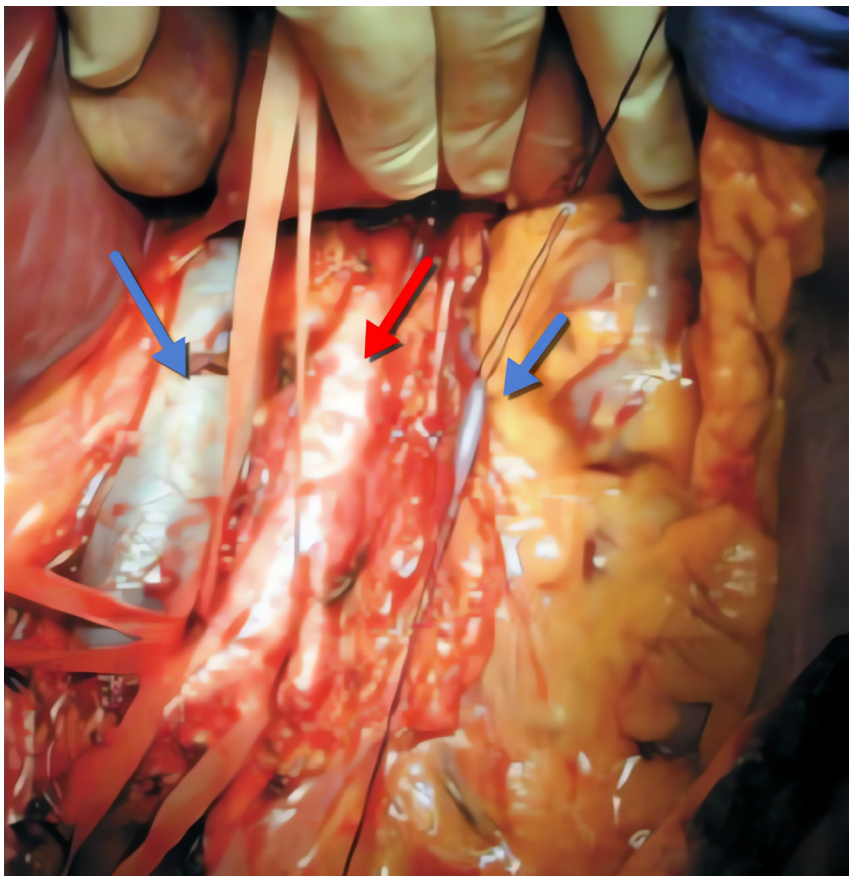

Figure 2. Dissection of infra-mesocolic retroperitoneum.

2.1 Bench surgery

To prevent preservation lesions, the duodenum-pancreatic graft must remain in the preservation solution under hypothermal conditions at 4ºC during bench surgery prior to implantation.

Splenectomy is performed, but splenic vessels should be ligated. Should the pancreas have been extracted with a lot of fat, this must be carefully removed, and the necessary ligations performed to minimize haemorrhage during reperfusion. It is advisable to invaginate the line of staples on the duodenal terminals (with continuous silk 3/0 suture, although this may vary according to group) to ensure maximum tightness of sutures and prevent ulterior fistulas.

In the event of coeliac trunk absence (common in joint liver and pancreas extractions), reconstruction of the pancreatic arterial vascularization will be necessary to enable good anastomosis with the recipient's iliac vessels. There are different vascular reconstruction techniques for the pancreatic graft:

1. **Y-shaped anastomosis:** anastomosis of pancreatic arteries with a segment of the donor's iliac bifurcation (Figure 2). Though it is the most widely used modality in the USA and Europe, the presence of two anastomoses increases the risk of arterial thrombosis.
2. **Termino-terminal spleen-mesenteric anastomosis:** Anastomosis between splenic artery and distal end of graft SMA (Figure 3). For some groups this is the technique of choice due to its simplicity [11]. The U-shape may be prone to kinking or reducing blood flow to the distal part of the graft.
3. **Termino-lateral spleno-mesenteric anastomosis:** Anastomosis between the splenic artery and graft SMA. This technique is rarely used.

On completion of bench work, the graft is arterially perfused with approximately 100 cc of preservation solution and is ready for implantation in the recipient.

Figure 3. Preparation of abdominal bench table.

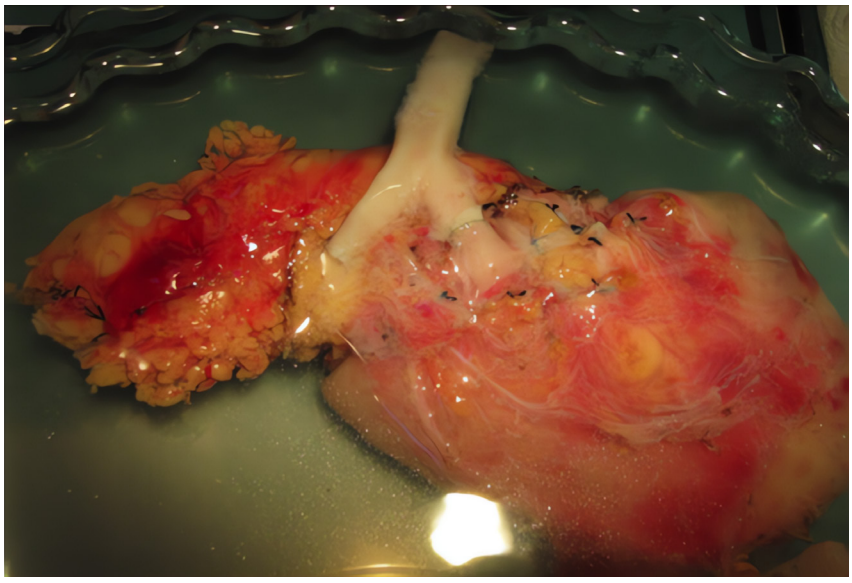

Figure 4. Arterial reconstruction of pancreatic graft via anastomosis.

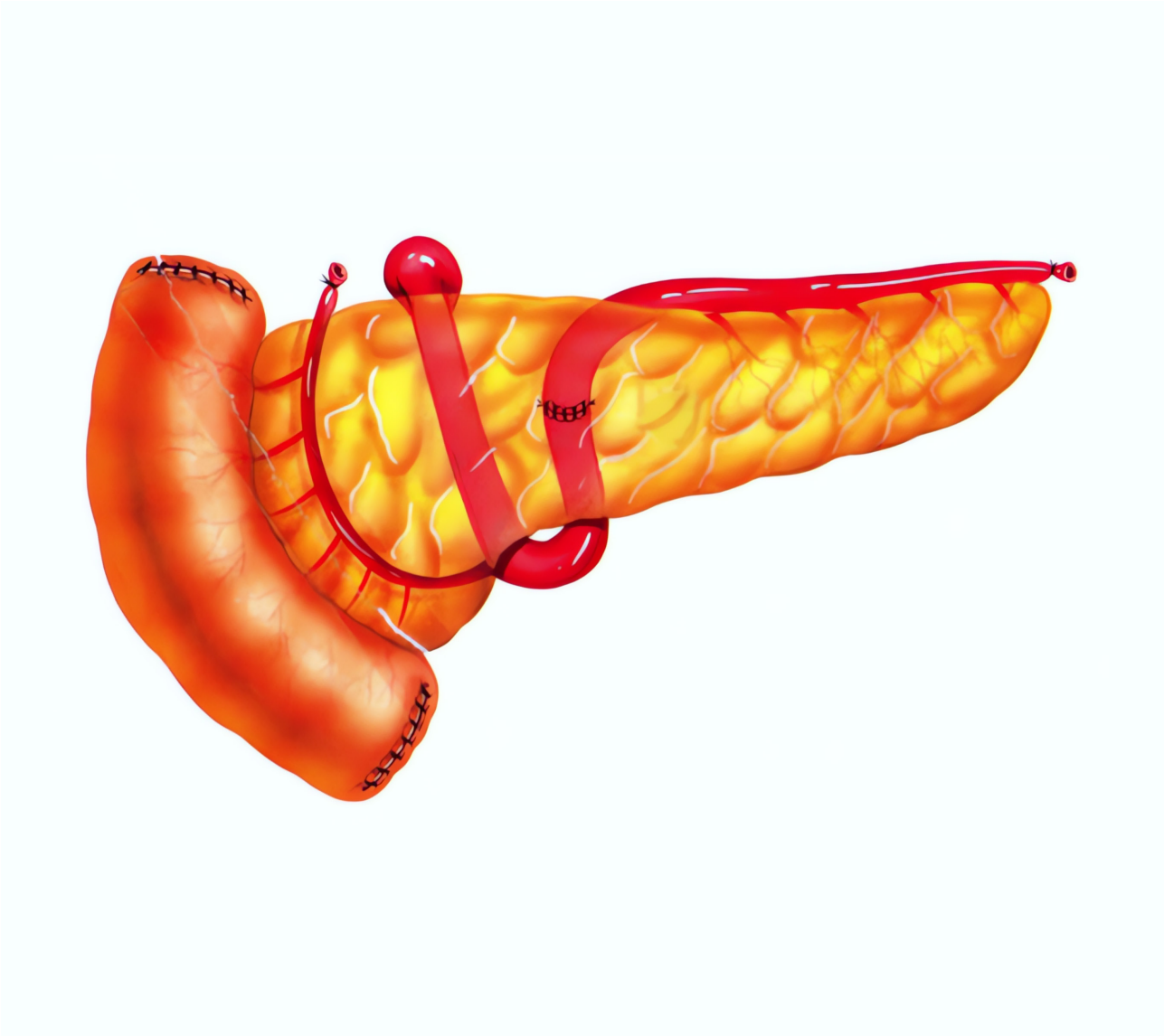

Figure 5. Arterial reconstruction of pancreatic graft via termino-terminal spleno-mesenteric anastomosis.

2.2 Preservation solutions

Preservation solutions are fluids with a specific composition designed to provide the essential nutrients needed for the cells in solid organ transplants to maintain their homeostasis, and reduce the risk of their swelling, lysis, and/or apoptosis during the CIT period (i.e., the period from organ retrieval from the donor and reperfusion with the recipient's blood after venous and arterial anastomosis).

Several preservation solutions are currently available in the market, each of which presents a different concentration and osmolality. The most commonly used are the University of Wisconsin (UW), Celsior®, IGL-1®, Bel-Gen®, ViaSpan®, and Custodiol HTK®. For pancreas transplantation, none of the solutions have demonstrated superiority over the others. Nevertheless, Custodiol HTK® has been reported as the least effective, with organs preserved with it presenting higher risk of early graft failure. Therefore, its use as preservation solution for this type of transplant is not currently advisable.

3. SURGICAL TECHNIQUE ON RECIPIENT

As previously described, SPK is the most common modality of pancreas transplant. Regarding implantation of the kidney graft, the surgical technique used is no different to that applied in kidney transplant alone. As to the pancreas graft, despite the lack of a standard surgical technique among centres, there is unanimous agreement on implantation of the whole organ, including the attached second duodenal portion.

Pancreas implantation

The pancreas is implanted before the kidney because it has less tolerance to ischaemia. The best transplant method is a supra-infraumbilical midline laparotomy, from a point halfway between the xiphoid and navel to 2-3 cm from the pubis. The complete pancreas, with a small portion of the donor's duodenum containing the ampulla of Vater, is placed laterally in the recipient's right iliac fossa. Placing the pancreas in the left iliac fossa increases the risk of graft thrombosis, due to the need for a longer vein, since the iliac veins and vena cava have the tendency to become dislocated to the right side of the body. Vein thrombosis is the most frequent cause of graft failure in the first week posttransplant.

Surgery begins with dissection of the ureter and right iliac vessels, which must be dissected and greatly mobilized to facilitate subsequent vascular anastomosis. Haemostasis is important, as is the ligation of larger lymph vessels. To facilitate venous anastomosis of the portal vein, mobilization of the distal vena cava and right iliac vein is advisable, ligating their posterior branches.

Once the iliac vessels have been dissected, the next step is to perform venous anastomosis between the graft portal vein and most proximal part of the right primitive iliac vein, even extending over the vena cava. Before anastomosis, the vena cava undergoes lavage with a solution diluted in heparin (1mg in 100 cc). Termino-terminal anastomosis between the portal and iliac veins should be performed using 2 continuous sutures with Prolene 5/0.

Next, arterial anastomosis is performed between the recipient's right primitive iliac artery and SMA or primitive iliac artery segment of the graft depending on the bench surgery used. At the start of the anastomoses, the interior of the graft must remain cooled via crushed ice compresses. On completion of arterial anastomosis vessels are unclamped sequentially, i.e., first the vein, then the artery, with the pancreas recovering normal colour immediately.

Systemic *vs.* portal nervous drainage

Systemic venous drainage (anastomosis to iliac vein or inferior vena cava) is the most common technique used. Some groups propose portal venous drainage for its hypothetical benefit of maintaining a more physiological insulin level. In systemic drainage, hyperinsulinemia —perceived by the patient as a hypoglycaemic episode (diaphoresis, transient sensation of faintness)— is quite frequent due to the graft's rapid release of insulin into systemic circulation in a response to glucose stimulus. In portal drainage, the hepatic passage of insulin mitigates these symptoms for patients. However, portal drainage is technically more complex, and its potential metabolic advantages are still controversial.

Enteric *vs.* urinary exocrine drainage

Pancreatic exocrine secretion may be urinary or intestinally drained. Table 1 shows the main differences between the two techniques.

Table 1. Urinary or intestinal drain of pancreatic exocrine secretion: Advantages and disadvantages of each technique.

	Urinary drainage	Intestinal drainage
Advantages	Safety (low risk of abdominal infection) Enables monitorization of rejection (determination of amylase and lipase in urine) Biopsy via cystoscopy is possible	Physiological drainage of pancreatic exocrine secretion Avoids urological complications
Disadvantages	Non-physiological drainage Urological complications (haematuria, cystitis, urethritis, urinary infection) Metabolic complications (metabolic acidosis, dehydration) Reflux pancreatitis	Monitorization of transplant rejection due to exocrine secretion impossible Septic intra-abdominal complication risk (peritonitis, abscesses)

Urinary drainage (duodenocystostomy) (Figure 6), contributed extraordinarily to the consolidation of pancreas transplantation since it enables rejection monitoring via determination of the pancreatic enzymes in urine. However, the high incidence of complications associated with this technique (metabolic acidosis, recurrent urinary tract infections), leads to reconversion to enteric drainage in up to 15-30% of cases. This is the reason why enteric drainage (duodenojejunostomy) (Figure 7), is currently the technique of choice.

Duodeno-enteric anastomosis is usually performed latero-laterally at jejunum level, at about 50 cm from the Treitz angle on two planes with continuous suture, one internal with Dexon® 3/0 and the other external seromuscular, with 3/0 silk. Use of a defunctionalized loop (Roux-en-Y) anastomosis increases complexity and does not improve graft survival or reduce the risk of fistula, so it is used less and less. On completion of the duodenojejunal anastomosis, lavage of the peritoneal cavity is performed with povidone iodine. Some groups perform the lavage with antibiotic solution to minimize the risk of peripancreatic infection and mycotic aneurysms.

Recently, some groups have described a duodeno-duodenal enteric anastomosis. In this technique, the donor's duodenum is anastomosed using a lateral-lateral suture with the second proportion of the recipient's duodenum. Arterial and venous anastomoses are performed as for duodenojejunal anastomosis. Authors advocate two particular advantages of this technique. First, the pancreas allograft is located in a retroperitoneal position, parallel to the inferior vena cava, which reduces its mobility and may therefore reduce the risk of thrombosis, kinking, or trauma. Secondly, an endoscopic approach to the donor duodenum increases the possibility of biopsy and diagnosis of rejection, CMV infection, or bleeding from the donor duodenum (a common cause of gastrointestinal bleeding in pancreas transplant recipients). Despite these advantages, some groups report an increased risk for graft thrombosis, and therefore this technique should be employed with caution.

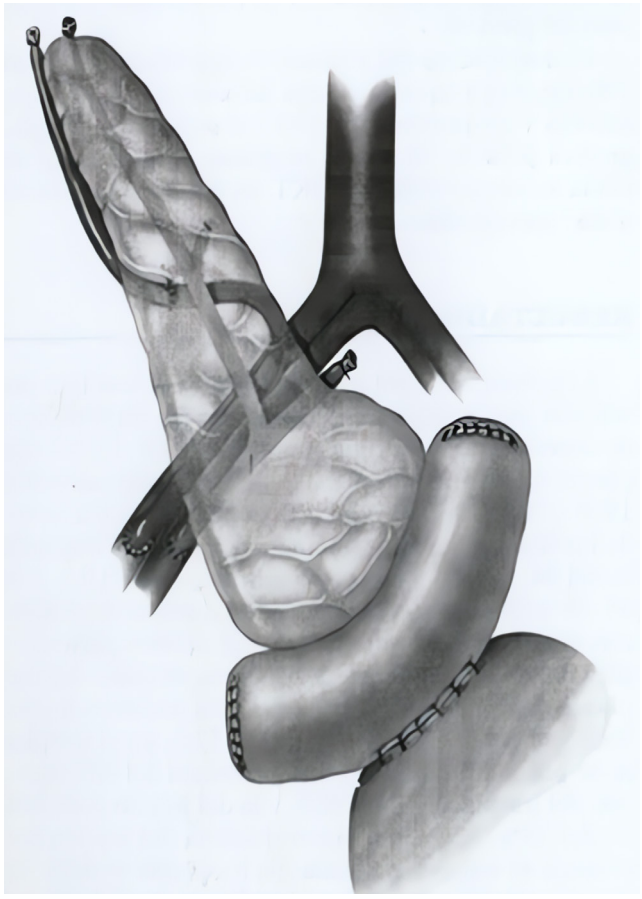

Figure 6. Pancreas transplant with urinary drainage of exocrine secretion.

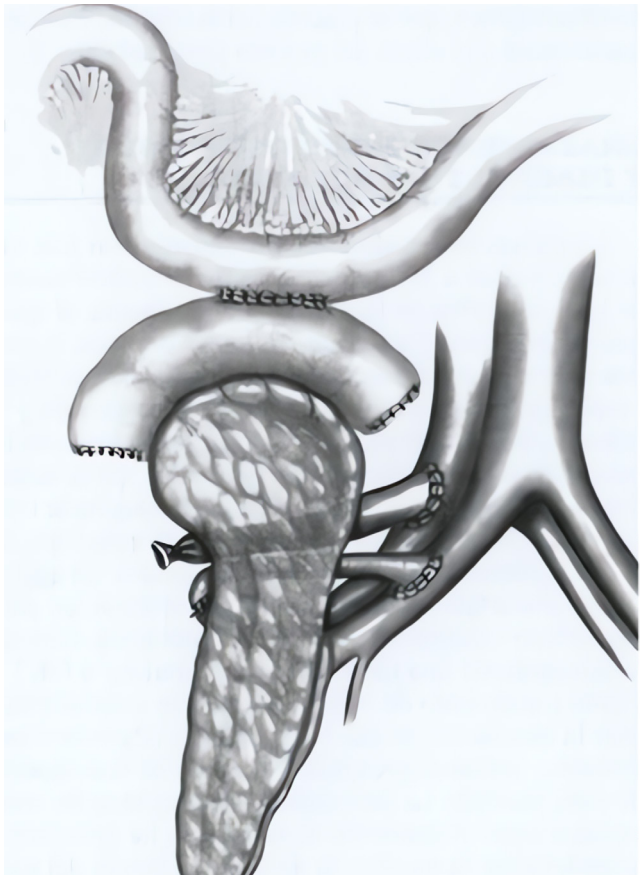

Figure 7. Enteric drainage (duodenojejunostomy) technique.

4. SURGICAL COMPLICATIONS

The main complications of pancreas transplantation (in addition to those that are common to all solid organ transplants) are due to certain of the organ's characteristics: low vascular flow and the exocrine component.

There are a series of factors which considerably increase the risk of presenting surgical complications, such as donor and/or recipient BMI of >30 kg/m^2, CIT >20 hours, non-traumatic death of donor, DCD, and to a lesser extent the intestinal drainage of pancreatic exocrine secretion.

Details of the main surgical complications follow:

Vascular complications

Arterial or venous thrombosis is one of the most common causes of premature graft loss (5-10%). The incidence of thrombosis is between 5-10% in SPK and 10-20% in PTA. Thrombosis is usually a venous thrombosis (60%), and onset occurs within the first days after transplantation.

The reasons for this are not well-known but have involved technical errors in performing vascular anastomoses, pro-thrombotic disorders and hypercoagulability, as well as microvascular lesions caused during graft extraction and preservation. Likewise, haemodynamic alterations reduce intrinsic flow from the organ, which in itself is low. Moreover, donor-related factors like age, cause of death or a prolonged ischemia period have also been associated.

The ideal diagnosis method for thrombosis is a colour Doppler ultrasound. An arteriogram will confirm the diagnosis in cases of partial or total thrombosis of pancreatic vessels and the use of interventionist radiology may also be necessary.

In complete thrombosis, emergency thrombolysis or thrombectomy must be performed using an endovascular approach with interventional radiology. Whenever this is not possible or when it fails, surgical thrombectomy or transplantectomy should be performed. In partial venous thrombosis, if the clot occupies over two-thirds of the vessel span, interventional radiology is the treatment and in the remaining cases, systemic heparinization. This has led to a reduction in graft loss due to venous thrombosis which is under 1%.

Other vascular pancreatic graft complications include haemorrhage, arteriovenous fistula and pseudoaneurysm formations, and also stenosis of the anastomoses.

Pancreatic fistulas

These usually occur at the anastomotic line level of the duodenal segment. Their incidence has reduced considerably in recent years, and currently fewer than 1% of grafts are lost due to this complication. Incidence ranges between 5-20% in bladder derivation and 5-8% in intestinal derivation. Early fistulas are generally attributed to ischaemia or technical failures, whereas later fistulas are usually due to infections or acute rejection. They are the second cause of relaparotomy after haemorrhage. Treatment depends on the type of exocrine secretion derivation and the importance of leakage.

Graft pancreatitis

Elevation of serum amylase is frequent after a pancreas transplant due to both donor-inherent factors and lesions caused to the pancreas during extraction, preservation, implantation and reperfusion. They are generally auto limited and do not usually have repercussions on organ function. Nevertheless, hyperamylasaemia may be indicative of real graft pancreatitis whose symptoms may include fever, abdominal pain, ileus and abdominal distension.

Pancreatitis occurring in the first weeks of transplant is usually secondary to acute rejection or infections (CMV). In patients with bladder derivation of exocrine secretion, they may also be due to urine reflux via the pancreatic duct. The following may result from graft pancreatitis: fistulas, peripancreatic collections or abscesses and pancreatic pseudocysts.

Infections

Infections are a frequent complication in this transplanted group (80% within the first year) and play an important role in graft and patient survival. Diabetes, surgery and immunosuppression are predisposing risk factors for infection in this population.

Pancreas transplant presents a risk of infection by CMV of 13-17%, largely due to the use of powerful antilymphocyte drugs: CMV infection is associated with increased mortality, rejection rates and the onset of other kinds of infection.

In addition to immunosuppression, diabetes and vasculopathy increase the risk of infection in these patients. Peritransplant antibiotic prophylaxis is advised. The incidence of infra-abdominal infections is 10-30%, the majority of which are polymicrobial, with fungi present in less than 10%. At our unit, we currently use prophylaxis against gram+ and gram- bacteria (ertapenem and vancomycin), CMV (valganciclovir) and fungi (fluconazole and co-trimoxazole). With this regimen established from the day of intervention, we have managed to reduce the short-term incidence of such infections. Nevertheless, monitoring is still necessary for a longer period to optimize management and treatment of these patients.

CONCLUSIONS

» A balance between donor criteria (comorbidity, surgical extraction, organ preservation and quality) and recipient selection and medical status always drives the quality of the transplant.

» In accordance with donor procedure, a favourable transplant outcome starts with an excellent evaluation of the donor.

» *In-situ* evaluation of the organ, its anatomic variations, and the technical aspect of the procurement and preservation directly determine the result of the pancreas transplantation.

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TOPIC 4 - Unit 3

Postoperative treatment and medical follow-up (early/late and histopathology/radiology)

ORGAN TRANSPLANTATION

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INTRODUCTION

The purpose of this unit is to discuss the postoperative treatment of pancreas transplant recipients, as well as the short- and long-term medical follow-up guidelines for this group of patients.

We review the most frequently indicated immunosuppressive treatment guidelines for pancreas transplant induction and rejection therapy. Likewise, we consider the prophylactic guidelines for treatment against certain infections or to prevent graft thrombosis, which are usually administered from the time of transplant.

The most frequent complications affecting these patients fall into two groups: those related to surgical technique, and those of an immunological or infectious origin.

Finally, we attempt to establish some short- and long-term guidelines for the control and follow-up of pancreatic transplant patients.

1. TREATMENT GUIDELINES

Pancreas transplantation is only feasible thanks to successful surgical techniques, and potent immunosuppression that prevents graft rejection by the recipient's immune system following organ reperfusion.

The previous unit described the technical aspects of pancreas transplantation. Here, we describe current immunosuppression protocols for pancreas transplantation, as well as the prophylaxis applied with the aim of reducing infection and thrombosis.

The impact of IS drugs on the metabolism of insulin should be carefully monitored. Patients should be strictly and intensively monitored during the first weeks after transplantation in order to establish a long-term balanced drug regimen for the transplanted patient.

1.1 Immunosuppressive treatment

Human immunity is a highly complex, evolved system, developed to protect the organism from external aggressors. As a response to an insult, the immune system is activated, and a cascade of events leads to deployment of the most effective response which will enable it to repulse the aggressor. After acute insult, the immune system often develops memory cells, which will enable a faster, more effective response in the presence of a second insult.

Organ transplantation involves both the innate (NK, macrophage, dendritic cells) and adaptive (T cells, B cells) immune system. Immune cells distinguish self from non-self cells through the major histocompatibility complex (MHC) molecules ubiquitously present on the cell surface. Current understanding is that human leukocyte antigen (HLA) is most often involved in allograft rejection.

The immune system presents a progressive response in the presence of an allograft. In brief, after organ reperfusion:

a) antigen presenting cells (APC) recognize the graft's HLA as non-self and secrete pro-inflammatory cytokines which will further recruit T, B, macrophage and NK cells to the affected area, while exposing its epitopes to CD4 T cells. Following their activation

b) T cells will adapt and continue the cascade, leading to

c) the expansion of epitope specific, cytotoxic CD8 T cells or B cells, accordingly. A sub-set will be

d) committed to memory cells and remain quiescent in the lymph nodes.

Knowledge of the immune system response to a transplant has led to the development of multiple therapeutic drugs which enable long-term graft survival. The main purpose of the different immunosuppression therapies is to control rejection, while at the same time minimizing graft damage and risk for the patient. In order to reduce the risk of side effects while maintaining the potency of immunosuppression, a combination of drugs is applied, during both the induction and maintenance periods. These are similar for all solid organ transplants, although the greater immunogenicity of the pancreas, particularly if the transplant is performed alone, means that the immunosuppression required is greater than in the case of a kidney, heart or liver transplant.

The incidence of acute rejection varies according to the transplant modality, with the highest rejection in pancreas transplant alone (PTA) recipients, followed by pancreas after a kidney transplant (PAK), and recipients of simultaneous kidney-pancreas transplant (SPK) experiencing least rejection.

Induction treatment

Induction treatment refers to potent immunosuppression given at high doses in the immediate post-transplant period (during the first week). It is usually initiated just before organ reperfusion.

High-dose corticosteroids (500 mg of methylprednisolone) are used in most solid organ transplants (SOT) a few minutes before reperfusion. The objective is to suppress immediate innate immune response.

However, induction therapy usually refers to the administration of polyclonal or monoclonal antibodies. In pancreas transplant, these are routinely included in immunosuppression protocols. Induction with these antibodies, as observed in various studies, reduces the incidence of acute rejection, delays its onset and reduces the number of steroid-resistant rejections.

The most frequently used therapies are T-cell depleting polyclonal antibodies (Thymoglobulin®/ATG-Fresenius®) and anti-CD25 (basiliximab; Simulect®) or anti-CD52 (alemtuzumab; Campath®) monoclonal antibodies. Although the first of these therapies present a reduced risk for complications (such as infections or lymphomas) their use may stop due to the increased risk of rejection and subsequent treatment with thymoglobulin. Therefore, despite an initial enthusiasm with both monoclonal antibodies, thymoglobulin is currently the most widely used induction therapy in pancreas transplant, with variations regarding total dose depending on transplant type (SPK or PAK/PTA). Retrospective studies from large series of patients have demonstrated a significant lower acute rejection rate and superior 1-year graft survival in recipients treated with thymoglobulin compared to treatment with monoclonal antibodies.

There is no standardized dose between reports, but a total dose of 6 mg/kg divided in 5 doses is advised for SPK, and up 8.5 mg/kg divided in 7 doses for PAK/PTA. These doses are often difficult to achieve due to medullar toxicity, with leucopoenia or thrombocytopenia.

Maintenance treatment

A combination of three drugs is generally administered in association with mono- or polyclonal antibodies and maintained in the long-term in pancreas transplant. This consists of a calcineurin inhibitor, an antimetabolite or mTOR inhibitor, and steroids.

Among calcineurin inhibitors, when it first became available, cyclosporine represented a new era in pancreas transplants. However, since its introduction, tacrolimus, has become the medication of choice. Different comparative studies show a lower incidence of acute rejection that is also less severe and is associated with better short- and long-term survival of the pancreatic graft in patients treated with tacrolimus.

The association of tacrolimus with an antimetabolite agent (mycophenolate-mofetil or sodium mycophenolate) has obtained excellent results and is currently the most used. Another option is to combinate tacrolimus with an mTOR inhibitor (sirolimus or everolimus). Although results obtained with this association seem superimposable, in terms of patient and graft survival, the incidence of complications attributable to rapamycin is greater in the immediate posttransplant period, so the combination is not so commonly used in this initial period. However, it is a good option in the long-term.

Aside from their use as induction therapy, different studies suggest that steroids can be suppressed as a maintenance therapy without affecting graft survival, particularly for patients receiving a calcineurin inhibitor associated with an antimetabolite or mTOR inhibitor.

Nevertheless, no consensus exists regarding their suppression due to the long-term impact it may involve. At present, it seems reasonable to withdraw steroids during the first 12 months for low immunological risk patients who do not experience episodes of rejection.

1.2 Prophylactic treatments

It is common practice to administer prophylactic treatment in pancreas transplant patients to prevent both graft thrombosis and certain infections.

Antithrombotic prophylaxis

Graft thrombosis is one of the most frequent early complications in pancreas transplant. Therefore, most transplant centres institute anticoagulant and anti-aggregation prophylaxis. Although variations exist between centres, a combination of low molecular weight heparin/unfractionated heparin and aspirin is most commonly used.

Antimicrobial prophylaxis

Infection continues to be one of the major causes of morbidity and mortality after pancreas transplant. Therefore, use of a wider prophylaxis is common in these patients. The following prophylaxis is recommended at the time of transplant and for a variable period of time thereafter:

- Antibacterial: wide spectrum antibiotics to cover negative and positive grams, and anaerobes. Used for 3 to 5 days and several associations are possible, generally cephalosporin + ampicillin or vancomycin.
- Antifungal: the most commonly used drug is fluconazole. Today, some prophylactic guidelines replace fluconazole with a new drug, micafungin, whose advantage is that it avoids interaction with tacrolimus.
- Antiviral: Most patients receive induction treatment with polyclonal antibodies, which are also known to increase the risk of infections, particularly viral ones. Prophylaxis is therefore recommended with valganciclovir in all recipient CMV infections.
- Anti-pneumocystis carinii: with trimethoprim-sulfamethoxazole for 6 months, as with kidney transplant.

2. COMPLICATIONS

The absence of complications after a pancreas transplant depends largely on detailed knowledge of both donor and recipient. In order to minimize morbidity, postoperative care begins presurgery and continues intraoperatively.

The first 24-48 hours are the most critical because the recipient is in most their vulnerable state. This stage involves three processes:

a) surgical trauma experienced by the patient;

b) ischaemia-reperfusion phenomena of the transplanted organ;

c) immunosuppression.

As might be expected, the combination of these 3 processes, particularly in a diabetic patient with complications secondary to DM, is a challenge for the medical and surgical team.

Surgical complications are relevant because they may lead to graft loss. From 1983 to 1987, 25% pancreas transplants performed worldwide were lost due to technical reasons. However, in the last decade, the percentage of surgical morbidity has dropped to less than 8% in high-volume centres.

Table 1. Summarizes the complications according to time of onset.

Table 1. Complications after pancreas transplant.

Complications
Pretransplant
Graft damage during organ extraction: » Lesion of vessels (splenic artery, SMA, portal vein) » Lesion of duodenum segment » Lesion of pancreatic capsule or parenchyma
Intraoperative
Recipient related factors: » Lesion of arterial vessels (iliac artery due to severe atheromatosis) » Haemorrhage due to venous vessel lesion (iliac vein) » Haemorrhagic pancreatitis in graft reperfusion » Incorrect graft perfusion » Cardiovascular morbidity
Posttransplant
Vascular complications: » Immediate graft thrombosis (60% venous, 40% arterial) » Late vascular complications (anastomosis stenosis, pseudo aneurysms, arterio-venous fistulas) » Vascular complications of kidney graft (in SPK)
Infections of surgical wound
Dehiscence of surgical wound
Intra-abdominal infection
Fistulas due to enteric or bladder anastomosis dehiscence
Graft pancreatitis
Pancreatic fistulas
Haemorrhage (intra-abdominal, bladder, gastrointestinal)
Urological complications (haematuria, dysuria, urethral complications, repetitive urine infections, etc.) in the case of urinary derivation of exocrine secretion
Infections (bacterial, viral, or fungal)
Lymphoproliferative diseases (lymphatic hyperplasia, lymphomas, etc.)

Unit 2 described the main complications that may be diagnosed after surgery.

3. CONTROL AND FOLLOW-UP

Pancreas transplant recipients are patients with a complex systemic disease that should be monitored closely on a regular basis following transplantation. The effects of diabetes and the potential impact of the transplantation open a new chapter for these chronically ill patients.

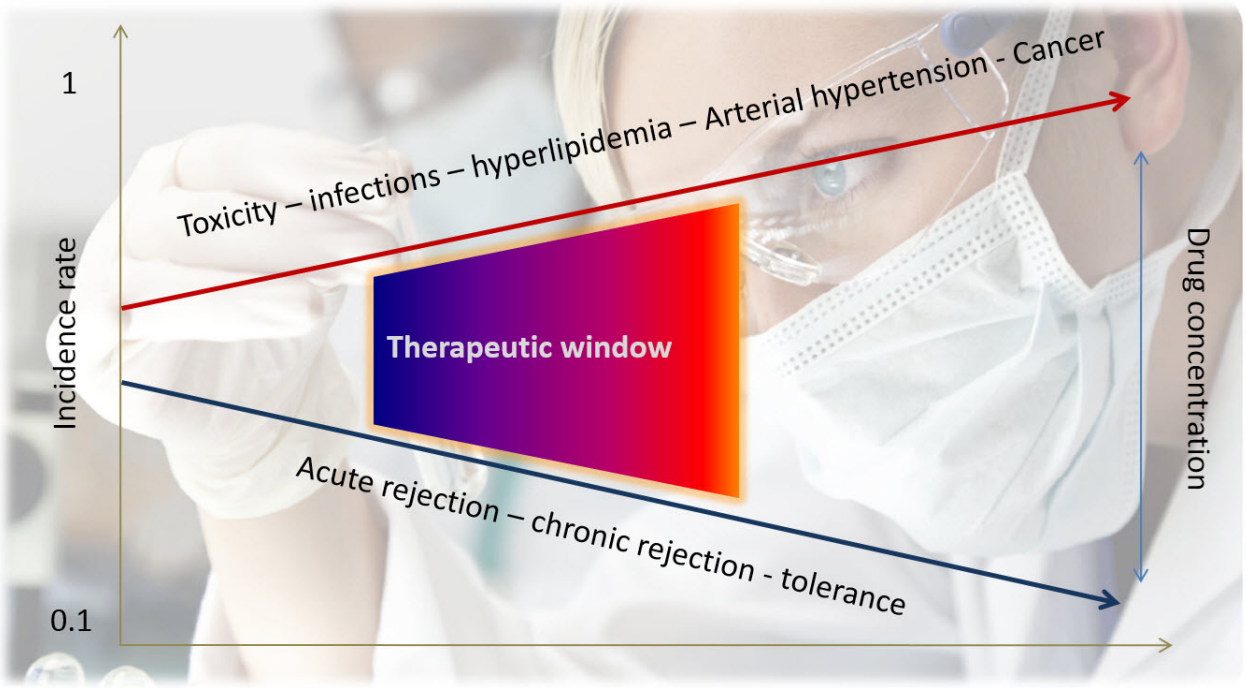

Figure 1. Therapeutic window.

3.1 Early control and follow-up

If we concentrate on the immediate postoperative period, there are a series of points to bear in mind:

Fluid management

Given the long history of diabetes in pancreas transplant recipients, coronary compliance and peripheral vessels may be compromised. Therefore, the optimum infusion volume during the immediate postoperative period must be carefully analysed. Although each case must be individually evaluated, maintaining a central venous pressure between 5 and 8 mmHg is considered correct. Administration of fluids with dextrose should be avoided since it may prolong the need for insulin.

Electrolyte management

In simultaneous kidney pancreas transplants, the salt and mineral balance must be monitored, particularly in the event of an immediate delay in graft function. Sometimes dialysis may be required in the early posttransplant period due to hyperpotassaemia.

Immunosuppression

See Section 1.

Antimicrobial prophylaxis

See Section 1.

Anticlotting and blood products

Many pancreas transplant recipients have anaemia before surgery. It is important to maintain correct haemoglobin levels (Hgb >10 mg/dl), particularly in the event of postoperative haemorrhage. There is a controversy regarding the need for immediate use of anti-coagulation.

Some centres use low doses of endovenous heparin, whereas other authors use low molecular weight subcutaneous heparin treatment associated with ASA, which will continue at home. It is important to monitor coagulation parameters to prevent "over-anticoagulation," since this may result in haemorrhage and the need for reintervention.

If not using anticoagulation there is a risk of early graft loss due to venous thrombosis and most authors agree that reoperation due to haemorrhage (low impact on pancreatic function) is preferable to thrombosis.

Monitoring patient's vital signs and haemodynamic state

Blood pressure is clearly related to fluid and electrolyte management. Both low and high blood pressure should be avoided. A systolic pressure of <100 mmHg increases the risk of graft arterial and venous thrombosis, in particular immediately post-surgery.

Further, severe prolonged HBP may lead to a cerebrovascular accident or acute myocardial infarction (AMI); it also increases the risk of intra-abdominal haemorrhage. It is advisable to maintain systolic pressure between 120 and 160 mmHg during the first 24 hours posttransplant to ensure correct graft perfusion and minimize the risk of adverse events.

Immediate graft function and evaluation

Immediate graft evaluation (in the case of SPK, both pancreatic and renal) may be monitored in different ways. The protocol accepted by most centres combines the study of laboratory parameters with imaging tests. Blood urea nitrogen (BUN), creatinine, amylase and lipase blood levels must be reduced, together with blood sugar levels within a normal range, for grafts to be considered correctly functioning (in the case of SPK).

In cases with exocrine drainage to the bladder, the amylase level in urine can be monitored. A reduction of 50% or more suggests rejection or pancreatitis. In enteric drainage cases, amylase and lipase blood levels provide additional information regarding pancreatic function. In the immediate postoperative period, pancreatic enzyme levels in blood may be high, with normal blood sugar levels, meaning ischaemia – reperfusion damage, which resolves spontaneously. In SPK, monitoring renal function and/or performing a renal biopsy have served to establish the diagnosis and treatment acute rejection, since for many years it was believed that, in most cases, acute rejection appeared simultaneously in both grafts.

However, today it is well-documented that rejection of one of the two organs occurs in over 30% cases. Pancreatic enzymes (amylase and lipase) are the only available biochemical markers to screen pancreatic graft rejection. Moreover, it is possible to observe changes in graft structure and size with ultrasound, or with an increase in resistance on performing a Doppler ultrasound in acute rejection cases. If there is a strong suspicion of acute pancreas rejection, percutaneous needle biopsy guided by ultrasound may be performed to establish a precise diagnosis.

To date, pancreas biopsy is considered the sole reliable diagnostic method to determine the aetiology of graft dysfunction. At our centre pancreatic graft biopsy is indicated in kidney-pancreas transplants or pancreas transplant alone in the following circumstances:

» Patients suspected of having acute rejection of pancreatic graft due to biochemical (increase in serous glycaemia, amylase and lipase) and/or ultrasound (increase in size, changes in graft eco-structure and Doppler affectation) parameters.

» Patients with suspected chronic rejection due to a persistent increase in serum amylase and lipase, progressive increase of glycaemia and HBA1c and/or progressive secretion of C peptide.

» Patients with suspected diabetic relapse due to detection or progressive increase of anti-GAD antibodies with oral glucose tolerance test (OGTT).

To establish the severity of the histological lesion of acute rejection, we use the Banff classification of rejection (2015 update). The Banff classification establishes parameters for cellular and humoral rejection, both acute and chronic, in addition to disease relapse or fibrosis.

Colour Doppler ultrasound (DCU)

This is the initial imaging technique of choice for pancreas transplant controls and follow-up. The DCU study enables evaluation of graft echostructure and size, presence of liquid collections (mode B study), parenchyma perfusion (resistance index), as well as permeability of vascular anastomoses (Doppler study). The study can be enlarged with an ultrasound signal booster if deemed opportune by the ultrasound technician. It is advisable to carry out a:

» basal study between 24-48 hours posttransplant;

» follow-up study every 3-4 days until patient discharge;

» in cases with fever, abdominal pain or pancreatic graft dysfunction.

Abdominal CT

This is indicated in cases where a DCU encounters technical limitations (abdominal distension, obesity) or there is a wish to extend the study.

It is advisable in the following situations:

» Patient with abdominal pain, fever and/or graft dysfunction, where DCU study is technically limited (abdominal distension, obesity).

» Intra-abdominal collection inaccessible to drainage via ultrasound.

» Intra-abdominal collection drained by ultrasound but without appropriate clinical response.

CT angiography

A CTA is indicated when bleeding or vascular pathology is suspected.

Advisable in the following situations:

» If the first posttransplant DCU test/s, did not provide an appropriate evaluation to confirm graft permeability (splenic and mesenteric artery/vein) due to abdominal distension, and dysfunction of persists.

» Serious haemorrhage from graft before surgery or otherwise, to establish origin thereof.

Arteriogram

This test is indicated to confirm diagnosis and/or treatment (thrombectomy) of partial arterial and/or venous graft thrombosis.

Vascular thrombosis monitoring

Thrombosis (essentially venous thrombosis) is the most frequent vascular complication of initial posttransplant (1-10 days after transplant). Therefore, its early diagnosis is important to commence appropriate treatment.

If the first posttransplant test/s do not provide findings that enable confirmation of graft permeability (splenic and mesenteric artery/vein) due to abdominal distension, the decision of whether to extend the study or not will depend on the functional state of the pancreas:

» Normal function: repeat study in 1-2 days.

» Dysfunction: study extended with a non-invasive imaging technique: CTA.

The protocol to follow upon diagnosis of vascular thrombosis varies according to centre and depends on the location and extension the thrombosis.

The patient usually remains in the ICU the first 48 hours posttransplant and is subsequently transferred to a conventional hospital ward provided there are no adverse effects. Oral intake is progressively introduced, and abdominal drainage removed. Before hospital discharge, a detailed description of medication and home care must be drawn up.

3.2 Long-term control and follow-up

Outpatient controls will be very frequent on hospital discharge, and gradually reduced if grafts present a normal or stable function. During the first 3 months, posttransplant control is usually weekly, then fortnightly until 6 months and monthly from 6 to 12 months. After one year the frequency of controls is decided in accordance with graft evolution. Controls will essentially concentrate on monitoring graft function and immunosuppression in addition to complications secondary to diabetes.

Functional graft monitoring

To evaluate pancreatic graft function, each outpatient control will involve a determination of basal glycaemia, glycated haemoglobin (HbA1c), as well as serum amylase and lipase.

During the posttransplant period, after hospital discharge, and again one year after transplant, an OGTT should be carried out. The guidelines regarding time periods for conducting subsequent follow-up OCTT vary between teams and centres.

Determination of C-peptide is also advisable to evaluate maintenance of insulin secretion throughout follow-up, as is anti-GAD determination to detect a possible relapse of diabetes. Both should be performed at least once a year.

Should rejection be suspected, a pancreatic biopsy is recommended when feasible because it is the only test which can confirm the existence, establish the type of rejection and indicate the appropriate treatment according to result.

A pancreatic biopsy would also be indicated should there be an increase in anti-GAD antibodies, to determine whether there is a relapse of diabetes. Sometimes the existence of such a relapse may condition maintenance of greater immunosuppression; however, it has not been established whether this treatment can stop the progression and thereby avoid consequent graft loss.

Immune monitoring and surveillance biopsies

The incidence of acute rejection is higher in pancreas transplant recipients compared to kidney transplants. Moreover, *de novo* donor-specific antibodies (DSA) have been associated with an increased incidence of rejection and graft loss. Some centres perform periodic screening with solid phase Luminex for class I and class II antibodies (every 3 months during the first year and annually thereafter).

Some centres also perform surveillance (or protocol) biopsies. Up to 30% of protocol biopsies find a sub-clinical rejection (absence of elevation of amylase, lipase, or glycaemia). At our centre, we currently perform surveillance biopsies at 3 weeks and 12 months posttransplant.

Immunosuppression monitoring

Most pancreas transplant recipients will undergo a double or triple therapy as maintenance suppression, which will gradually be reduced and adjusted during follow-up to prevent long-term side effects.

To perform dose modifications with greater safety, it is advisable to monitor immunosuppressive drugs at each control. We thus ascertain whether the patient's levels are within the appropriate range for the transplant time, their specific characteristics, or if there is an immunosuppression deficit.

During each visit, it is important to check whether the patient is complying with their treatment and insist on the importance of compliance to prevent a potential rejection. Moreover, we must also check for possible side effects of the medication, and the toxicity of immunosuppressive drugs. The great incidence of neoplasia attributable to them means that we must be alert to possible skin lesions. It is likewise important to perform chest X-rays and abdominal ultrasounds periodically throughout follow-up.

Control of complications secondary to diabetes

Once a patient has received a pancreas transplant, they must continue to undergo control and follow-up for complications secondary to diabetes which, in most cases, was already present before the transplant.

To this effect, it is advisable that patients undergo an annual ophthalmological examination and receive a regular neuropathological assessment of both the peripheral and autonomous nervous systems according to severity. We should likewise be particularly alert for complications related to vasculopathy (the onset of precordial pain, ischaemic type lesions in lower limbs).

Hygiene/dietary measures

During follow-up it is also advisable to remind the patient about the importance of a series of hygiene or dietary measures to help prevent possible complications.

Among these, recommendations should include:

- Following an appropriate diet to prevent weight gain.
- Encouraging physical exercise.
- Avoiding exposure to the sun.
- Prohibiting or limiting alcohol consumption, depending on the case.
- Recommending appropriate footwear to prevent friction and undergoing periodic podiatric control.
- For women of childbearing age, recommending contraception options to prevent pregnancy during the first 1-2 years after transplant.

CONCLUSIONS

» Induction therapy with ATG, together with tacrolimus, mycophenolate-mofetil and steroids is the most widely used immunosuppressive treatment for pancreas transplant recipients. Different studies suggest corticoids may be withdrawn without affecting graft survival, although currently there is no consensus.

» At the same time, it is standard to apply prophylactic treatment for thrombosis and infections, such as bacterial, viral and fungal infections.

» Pancreas transplant is a procedure which improves quality of life in the long term. To achieve success in stabilizing the complications secondary to DM, long-term graft function also depends on a postoperative process free of complications.

» Given the complexity of type 1 DM patients, all peri- and postoperative aspects must be carefully monitored to keep the graft functioning for as long as possible.

» For long-term control and follow-up, functional monitoring should be carried out of the graft, immunosuppression, and possible complications derived from immunosuppressive drugs, as well as complications secondary to diabetes.

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TOPIC 5 - Unit 1

Indications and waiting list

ORGAN TRANSPLANTATION

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2. RISK FACTOR EVALUATION AND CONTRAINDICATIONS 225
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INTRODUCTION

Despite advances in treatment of advanced heart failure (HF), the mortality of this condition continues to be high. For a select group of patients, heart transplant (HT) is the sole treatment alternative [1]. In patients with refractory HF, American Heart Association/American College of Cardiology (AHA/ACC) stage D, HT provides an important improvement in survival and quality of life, provided correct recipient selection criteria are applied.

The two major limitations affecting HT are the insufficient number of donors and HT contraindications in candidate recipients [2].

This chapter clearly and straightforwardly analyses the minimum essential knowledge necessary for any doctor to treat transplant-susceptible patients and HT recipients.

This section includes:

- A systematic study of the refractory heart failure population to establish the indications and contraindications for heart transplant.
- Information about the tools to assist in dealing with the waiting list, assessment of appropriate donors and recipients.
- A review of basic and advanced surgical techniques for extraction and implantation, in addition to perioperative and immediate postoperative complications.
- An analysis of the main follow-up problems of a transplanted patient and update treatment guidelines to achieve better long-term results.

1. PROGNOSTIC EVALUATION IN CONGESTIVE HEART FAILURE

When assessing the prognosis of outpatients with chronic HF, the major determining factor for HT waiting list inclusion is a serious limitation of functional capacity. The cardiac stress test with determination of maximum oxygen consumption (VO_2 max) is the most objective method for evaluating functional capacity and the one which best correlates with prognosis [4].

A VO_2 max >14 mL/kg/min is associated with survival at 1 year similar to that of HT, whereas a VO_2 max <10 mL/kg/min implies high short-term mortality. Currently, the indication for HT is a VO_2 max <10-12 mL/kg/min although if it is >14 mL/kg/min the patient should preferably continue with medical treatment since HT would give no benefit in terms of survival at one year.

However, VO_2 max values should never be the sole criterion for including a patient on the HT list. Other parameters such as determining functional class via the NYHA classification, a very reduced left ventricular ejection fraction (LVEF) (<20%), repeated hospitalizations due to HF, persistent extremely high natriuretic peptides, HF of ischaemic aetiology, the presence of ventricular arrhythmias, maintained hypotension, a low cardiac index (<2.5 l/min/m^2) or hyponatraemia (<130 mEq/l) have been associated with a worse HF prognosis. While each of these on its own may not be an indication for HT, they may be useful for decision making in intermediate circumstances (VO_2 max >12 y <14 mL/kg/min) [5,6].

Prognostic scores such as the Heart Failure Survival Score (HFSS) have been developed that may be useful when deciding the indication for HT [7]. This system is based on the analysis of 7 variables usually obtained on evaluating a patient as a HT candidate: ischaemic aetiology, intraventricular conduction defects, heart rate at rest, mean BP, LVEF, VO_2 max and serum sodium. Patients with a high risk score (HFSS <7) are those who present a higher prognostic benefit with HT. This score is calculated according to the following equation:

HFSS = ([0.0216 × heart rate at rest] + [−0.0255 × mean arterial blood pressure] + [−0.0464 × left ventricular ejection fraction] + [−0.0470 × serum sodium] + [−0.0546 × peak VO2] + [0.6083 × presence (=1) or absence (=0) of intraventricular conduction defect (QRS interval ≥120 ms due to left or right bundle branch block, nonspecific intraventricular conduction delay, or ventricular paced rhythm)] + [0.6931 × presence (=1) or absence (=0) of ischaemic cardiomyopathy]); the 7 products are added and the absolute value is taken as the HFSS. The HFSS values associated with each risk stratum are ≥8.10 for low risk, 7.20 to 8.09 for medium risk, and ≤7.19 for high risk.

Beta-blocker therapy has changed the decision-making configuration (Figure 1) and as the International Society for Heart and Lung Transplantation (ISHLT) recommendations for its use or otherwise show, it may condition different cut-off points in the indication.

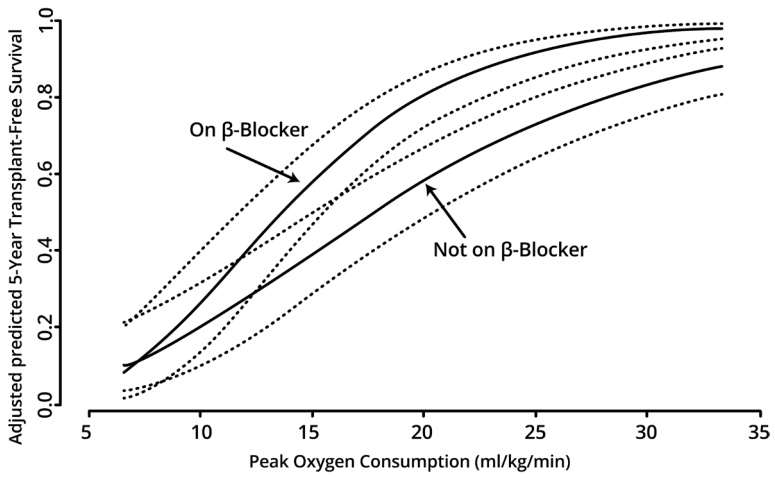


Figure 1. Betablocker therapy.

The latest indications established by the ISHLT for HT are [8]:

- In patients treated with beta blockers, a cut-off point of VO_2 max <12 mL/kg/min should be used as a guideline to indicate HT (recommendation degree I, evidence level B).
- In patients with beta-blocker intolerance, a cut-off point of VO_2 max <14 mL/kg/min may be recommended for HT (recommendation degree I, evidence level B).
- In intermediate circumstances (VO_2 max >12 y <14 mL/kg/min), we can consider using the HFSS in prognosis evaluation as a guide for indicating HT in outpatients (recommendation degree IIb, evidence level C).
- In young patients (<50 years) and women, the use of alternative parameters is recommended in addition to the absolute value of VO_2 max to guide HT indication, such as a percentage (≤50%) of the expected VO_2 max value depending on patient (recommendation degree IIa, evidence level B).
- Patient inclusion on the HT list should not be based solely on VO_2 max value (recommendation degree III, evidence level C).

Other less common elective HT indications are symptomatic ventricular arrhythmias that are unresponsive to medical, surgical or implantable defibrillator treatment, severe ischaemia with limitations in performing daily activity that are not susceptible to surgical or percutaneous revascularization. Table 1 shows the HT indications included in the AHA/ACC HF treatment guides [2].

Table 1. AHA-ACC HT indications

I Absolute indications

- Haemodynamic deteriorations due to heart failure
  - Refractory cardiogenic shock
  - Proven dependence on IV inotropic support for correct organ perfusion
  - Peak VO_2 <10 mL/kg/min having reached anaerobic threshold
- Severe myocardial ischaemia with limitation of daily activities that is not susceptible to surgical or percutaneous revascularization
- Recurrent symptomatic ventricular arrhythmias to all therapeutic modalities

II Relative indications
- Peak VO_2 11-14 mL/kg/min (or 55% of expected) and serious limitation of functional capacity - Recurrent unstable ischaemia not susceptible to another intervention - Recurrent instability of fluid balance/renal function not due to therapeutic non-compliance
III Insufficient indications
- Low LVEF - History of previous NYHA functional class III or IV - Previous ventricular arrhythmias - Peak VO_2 <15 mL/kg/min (greater than 55% of expected) with no other indication

2. RISK FACTOR EVALUATION AND CONTRAINDICATIONS

Contraindications for HT are conditions which alone or combined may significantly increase post-HT morbidity and mortality. In the past, contraindications were absolute and relative; however, over time the concept of an "absolute" contraindication has evolved, and the preference is currently to consider conditions that increase post-HT morbidity and mortality (Table 2). These conditions should be evaluated as a whole, and the decision to contraindicate HT should be made on a patient-to-patient basis [9].

Table 2. Risk factors associated with greater HT morbidity and mortality

» Age generally >70 years ("biological" prevails over "chronological" age)
» Malignant neoplasms with a high probability of recurrence after immunosuppressive treatment
» Active infection
» Diabetes mellitus with severe involvement of target organ
» Smoking, alcohol and/or drug addiction
» Unfavourable psychosocial environment impeding adherence to treatment or post-HT follow-up
» Severe renal or hepatic disfunction unless susceptible to combined transplant
» Severe fixed PHT
» Obesity
» Severe cerebral or peripheral vascular disease
» Peptic ulcer or active diverticular disease
» Recent thromboembolism
» Other systemic diseases with bad prognosis

In the haemodynamic study of HT candidates, an evaluation of pulmonary hypertension (PHT) via right side catheterization is critical to determine post-HT risk [10]. A PHT, defined as an average pulmonary pressure of >25 mmHg is an independent predictor of post-HT mortality. In a pre-HT evaluation, other important elements are determination of transpulmonary pressure gradient (TPG - the difference between mean arterial pulmonary pressure and capillary pulmonary pressure) and pulmonary vascular resistance (PVR = TPG / cardiac output).

In patients with left chronic HF and maintained elevation of left ventricle telediastolic pressure (LVTDP) is transmitted retrograde towards the pulmonary vascular bed, producing passive elevation of PAP and reactive vasoconstriction of the pulmonary bed. Elevation of PHT and PVR are initially reversible, responding quickly to both pharmacological and mechanical measures, which discharge the left ventricle, and to the use of vasodilators. However, when this process continues, a pathological remodelling of pulmonary vessels occurs, which involves a fixed elevation of PVRs, so the PHT finally becomes irreversible. Identification of which of the 2 components predominates in an HT patient candidate is of vital importance.

Although reversible, PHT and PVR elevation enable pharmacological treatment post-HT, but when they become essentially irreversible, they constitute an unsurmountable obstacle that determines right ventricle failure of the graft, prohibitively increasing morbidity and mortality.

Post-HT risk increases significantly when PVR >3 Wood units (WU) and TPG >14 mmHg. Although the cut-off point is undefined, it is usually from PVR >5 WU and TPG >16 mmHg and HT is considered contraindicated. When a reduction in pulmonary pressures to TPG <12 mmHg and PVR <3 WU is achieved with use of test drugs with inotropes and/or vasodilators PHT is considered reversible. If the PHT is predominantly reversible, risk is considerably reduced, which enables HT to go ahead with acceptable success rates. Use of pulmonary vasodilators in these patients (e.g., sildenafil, bosentan) seems promising. Although these drugs have yet to appear in the recommendations of clinical practice guides, several published studies have suggested the potential benefit of these drugs [11].

Finally, Figure 2 presents an algorithm for guidance of decision making when choosing HT candidates. The diagnosis/prognosis studies recommended in the pre-HT study to establish HF prognosis and identify risk factors, and the situation with a view to prophylaxis or treatment of infectious diseases can be consulted in the literature on this subject, such as the Consensus Conference of Spanish Heart Transplant Groups [9].

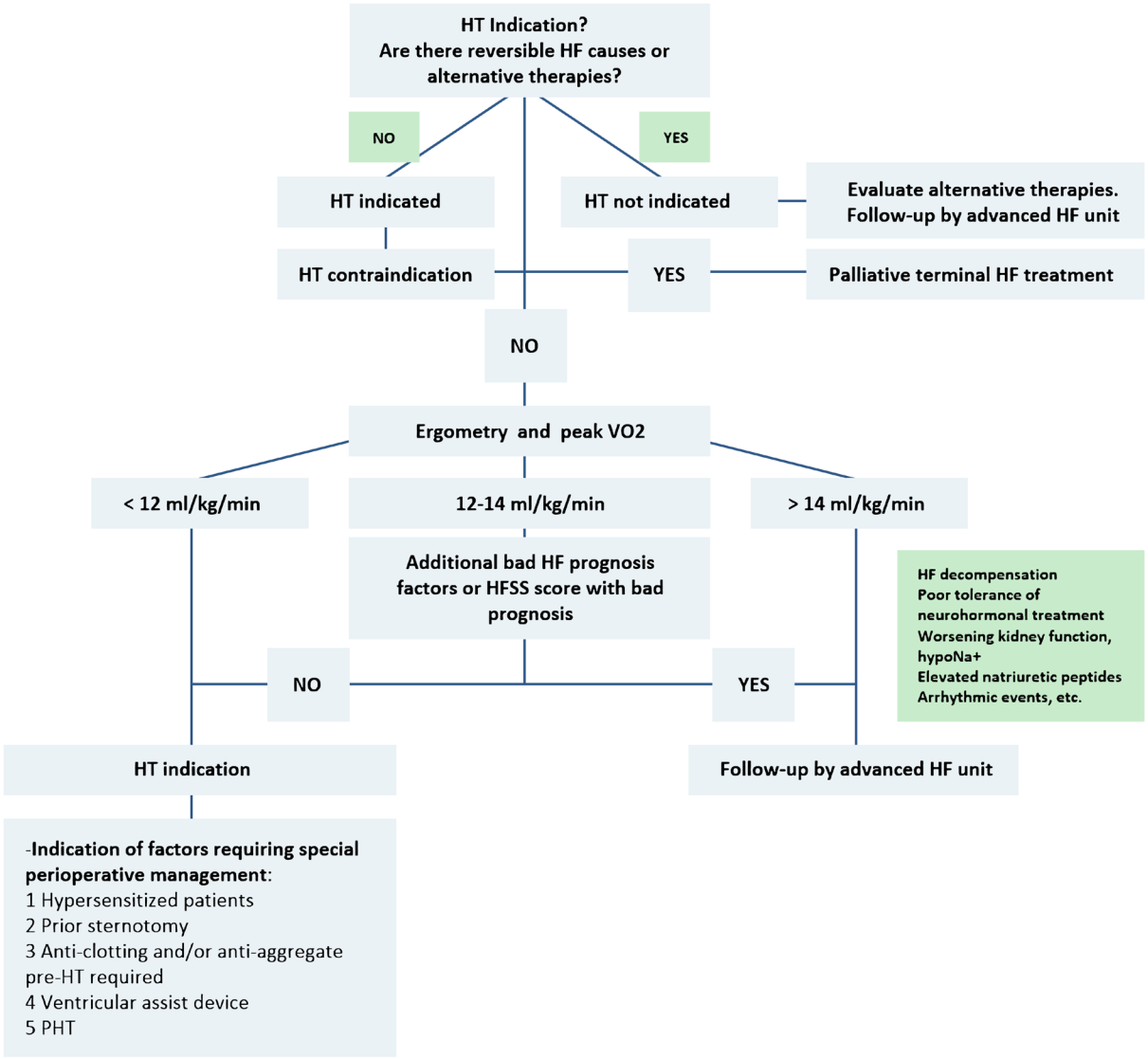


Figure 2. HT indication algorithm.

3. DECISION-MAKING FOR THE WAITING LIST

The indication for urgent HT has progressively increased in recent years, amounting to 38% of HTs performed in Spain in 2011 [3]. Figure 3 shows the development of urgent versus elective transplant percentages in recent years in a standard Service.

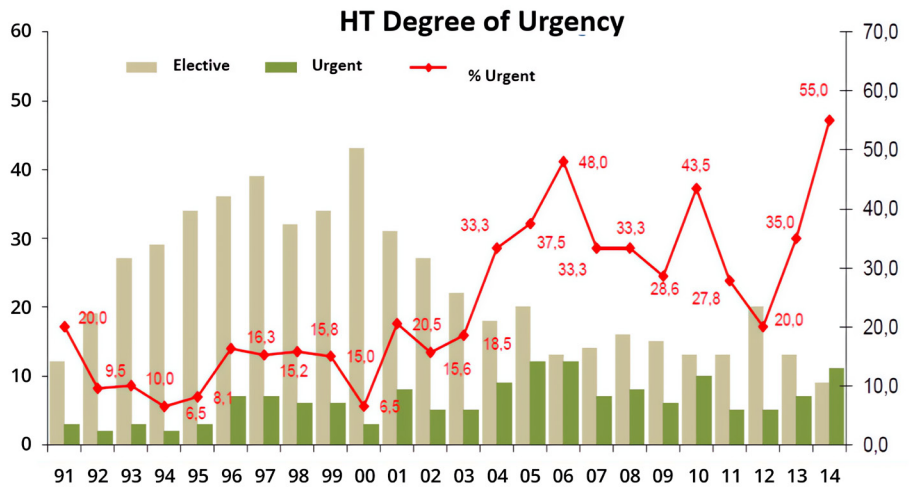
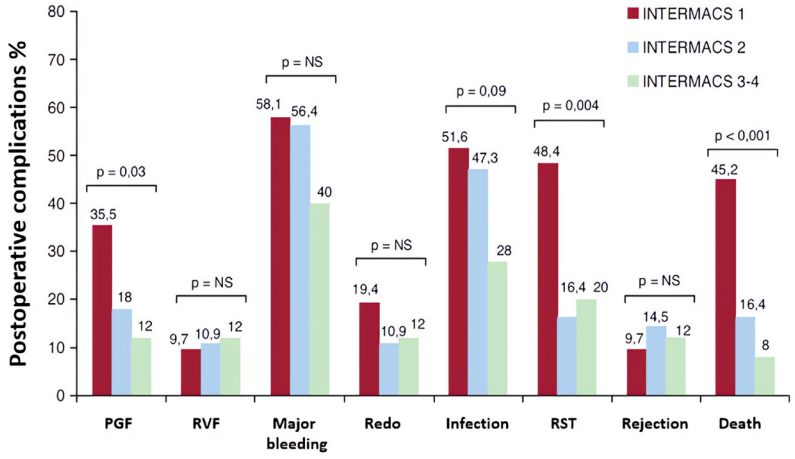


Figure 3. HT Degree of Urgency.

The criteria for including a patient on an urgent HT list are decided by consensus among the Spanish HT groups and National Transplant Organizations (NTO). Today, this indication is accepted for patients in irreversible refractory cardiogenic shock requiring ventricular assistance, intra-aortic balloon pump (IABP), with high doses of vasoactive drugs and mechanical ventilation.

For the success of urgent HT and optimization of resources, patients with an unacceptably high risk should be excluded. In particular, this refers to patients with multi-organ failure (defined as two or more affected organs plus a progressively deteriorating cardiovascular condition despite treatment). This is even more the case if sepsis is suspected, since there would be no benefit from an urgent HT, so it is usually contraindicated in these circumstances. The INTERMACS scale (Table 3) is also a useful tool for stratifying postoperative prognosis after an urgent HT [12,13]. Figure 4 shows the relation between high-risk patients (INTERMACS 1 and 2) and a high post-surgical complication rate and/or death.



PGF: primary graft failure; RVF: isolated right ventricle failure; NS: no significative differences; Redo: surgical reintervention; RST: renal substitution therapy.

Figure 4. Incidence of postoperative complications of patients included in the study.

Table 3. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Levels

Level[a]	Haemodynamic status
1 "Crash and burn"	Persistent hypotension despite rapidly escalating inotropic support and eventually IABP, and critical organ hypoperfusion.
2 "Sliding on inotropes"	Intravenous inotropic support with acceptable values of blood pressure and continuing deterioration in nutrition, renal function, or fluid retention.
3 "Dependent stability"	Stability reached with mild to moderate doses of inotropes but demonstrating failure to wean from them due to hypotension, worsening symptoms, or progressive renal dysfunction.
4 "Frequent flyer"	Possible weaning of inotropes but experiencing recurrent relapses, usually fluid retention.
5 "Housebound"	Severe limited tolerance for activity: comfortable at rest with some volume overload and often with some renal dysfunction.
6 "Walking wounded"	Less severe limited tolerance for activity and lack of volume overload. Fatigues easily.
7 "Placeholder"	Patient without current or recent unstable fluid balance. NYHA class II or III.

Abbreviations: IABP, intra-aortic balloon pump; NYHA, New York Heart Association.

[a] Life-threatening arrhythmias or active ischaemia may be the primary limitation to function at any of these stages of disease, thus modifying the INTERMACS level, in which mechanical circulatory support allows intensification of other therapies, such as beta blockers.

Table 4. contains the ONT 2014 (www.ont.es) waiting list priority clinical data for adult donor distribution.

Priority clinical criteria on ONT waiting list for donor distribution	
Unstable clinical situation	
Urgency 0 National priority	1. Ventricular assist device or short-term ECMO (≤30 days) 2. Long-term ventricular assist device (>30 days) dysfunction due to mechanical dysfunction, infection or thromboembolism
Urgency 1 Priority over other grade 1 urgencies of other regions and national elective HT	1. Cardiogenic shock requiring at least 1 of the following: » Vasoactive drugs and mechanical ventilation. with invasive intubation » IABP with/without associated intubation » Long-term ventricular assist device (>30 days) 2. Patients in arrhythmic storm situation
7 "Placeholder"	Patient without current or recent unstable fluid balance. NYHA class II or III.
Stable clinical situation	
Elective	» Stable patient eligible for HT waiting list inclusion

Recent years have seen a drop in the number of donors and an increase in age of both donors and recipients. This means there has been a qualitative change in waiting list management, together with a greater percentage of emergency situations. Furthermore, a more refined handling of terminal heart failure means more recipients are closer to a situation of contraindication. As a result, we now have a need for medium- and long-term circulatory assist devices to bridge the gap of a longer wait, to adapt to changes in transplantability conditions or as a definitive therapy.

Currently, the number of patients receiving therapy with these circulatory assistance systems is reaching a balance with the number of transplanted patients worldwide.

In addition to a reduction in the number of donors, there have also been changes in cause of death. Some years ago, the most common donor was a young patient who had died in a traffic accident. A reduction in the number of traffic accidents in conjunction with improvements in traumatic brain injury treatment mean that currently the most common cause of donor death is stroke. Figure 5 shows the donor typology of a transplant group (CHUAC) in recent years.

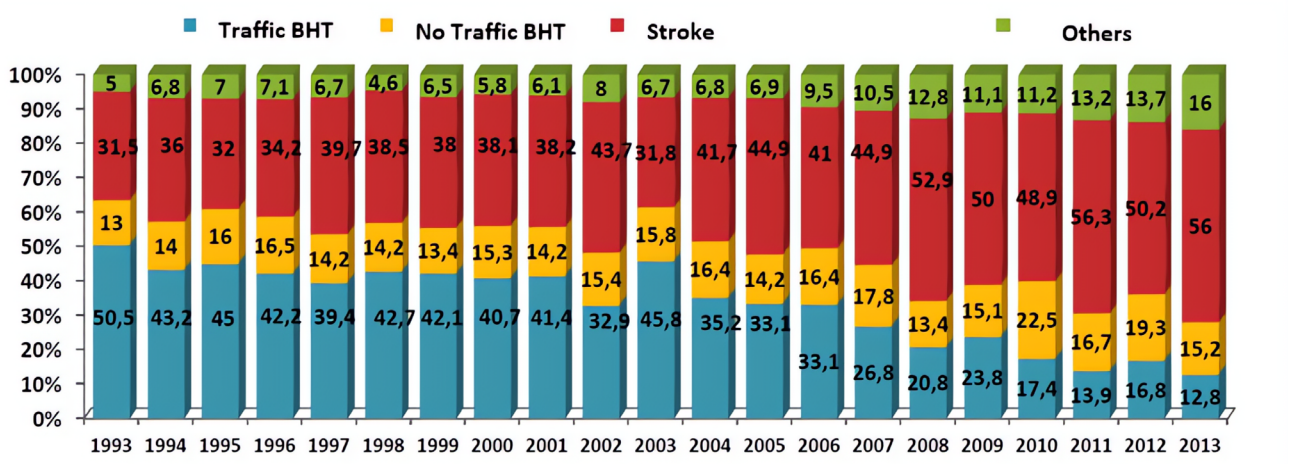


Figure 5. Cause of death.

As a result, in the present and in the immediate future we face a complex panorama consisting of:

- » older donors with more comorbidities;
- » older recipients with comorbidities, taken to the limit of transplant indication;
- » a higher percentage of urgent transplants (due to older donors and recipients);
- » a higher percentage of transplants with circulatory assist devices;
- » greater initial complexity and possible greater premature deterioration of grafts;
- » we must endeavour to optimize our decisions regarding patients on the waiting list to the maximum.

CONCLUSIONS

» Oxygen consumption is one of the most useful tools in terminal heart failure prognosis evaluation, although it should not be the sole criterion for consideration when decision making. There are scales and new indicators which may and should support our decisions.

» The decision for transplant indication/contraindication should be made by the team on a patient-by-patient basis. High PVRs constitute a classic risk factor, although with the arrival of new drugs and advanced circulatory assist devices opens up a new horizon for these patients.

» Correct donor selection for the ideal recipient is of maximum importance. At present, this situation is increasingly complex due to the change in donor profiles, with more added risk factors (age, pathology) and changes in recipient profiles, with more comorbidities and greater frequency of urgency/emergency situations requiring the use of circulatory assist devices.

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TOPIC 5 - Unit 2

Organ evaluation and surgical procedure (techniques and surgical complications)

ORGAN TRANSPLANTATION

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INTRODUCTION

Selecting the correct donor for the correct recipient is one of the key elements of the heart transplant (HT) process. This chapter offers recommendations for the selection of a good graft and ways to optimize its performance.

We will review the main surgical techniques for both donor explant and recipient implant, analysing possible benefits and complications.

Finally, we emphasise the idiosyncrasies of intraoperative and immediate postoperative management, leaving long-term follow-up aspects for forthcoming chapters.

In this section we review the following items:

- Criteria for optimum heart donor and necessary categorization tests.
- Donor maintenance and optimization strategies during the harvesting process.
- Acquisition of knowledge about the main harvesting and surgical implant techniques, evaluating the differences, advantages and drawbacks of each.
- Knowledge of the main early postoperative complications and how to deal with them.

1. ORGAN EVALUATION AND HARVESTING

Donor selection is a very important step in the success of a heart transplant. A series of criteria exists under which a patient may be deemed not optimum as a heart donor, although many are not absolute contraindications and therefore must be carefully studied [1-3].

Factors to consider in any prospective donor are [1,4]:

- age and cause of death
- cardiovascular risk factors
- important comorbidities
- blood group compatibility
- body surface
- hours in ICU and inotropic support required
- infection data
- existence of cardiac arrest or thoracic trauma
- distance

Necessary tests a donor must undergo [1,5]:

- ECG
- Chest X-ray
- Analysis with HIV, HCV, HVB serology
- Myocardial damage marker serialization: We must bear in mind that with brain death, and due to the existence on occasion of prior cardiac arrest, myocardial markers may be altered. Therefore, an increase in myocardial markers should be treated with caution and considered alongside echocardiographic findings [6].
- Transthoracic echocardiogram [5,7,8]: This is possibly the test with the biggest influence on decision. We may observe the following:
  - Presence of anomalous heart structures invalidating heart donation: cardiomyopathy, structural heart valve disease or significant congenital defects.
  - Absence of structural anomalies. In this case, the final factor evaluated is the systolic function of both ventricles (essentially the left) generally obtaining:
    - EF >60%. Heart is valid.
    - EF ≥50% in presence of non-dilated non-hypertrophic heart. Heart is valid for transplant.
    - EF 40-50% in the absence of dilation or any other structural anomaly. The echocardiogram should be repeated in 2-4 hours. If the myocardium has recovered after this time lapse to an EF ≥50%, the heart will be valid for transplant.
    - EF <40% in the absence of dilation or any other structural anomaly. Subjects with an initial ejection fraction <40% might exceptionally be considered donors.
  - In general terms, a transoesophageal echocardiogram is unnecessary, although it may be performed if there are any doubts regarding the existence of a structural anomaly.

- Coronary angiography: Controversy exists regarding atherosclerotic disease evaluation in heart donors, although it has been proven that atherosclerotic disease is present to a certain degree in 50% of donors over the age of 40. Generally, in patients over 50 years, particularly if there are cardiovascular risk factors, it is advisable to ascertain the condition of their coronary arteries. However, given both the patient's critical condition and centre logistics, many centres do not perform a coronary angiography on any donors [9,10].
- Traditional heart donor eligibility criteria [11]:
- Under 55 years
- Absence of prior cardiopathy or chest trauma with myocardial involvement
- Absence of hypotension or prolonged hypoxemia
- Correct haemodynamics:
  - Mean arterial pressure over 60 mmHg.
  - Central venous pressure between 8 and 12 mmHg.
  - Inotropic support below 10µgr/kg/min (dopamine or dobutamine).
- Normal ECG
- Normal echocardiogram
- Negative serology (VIH, HBV, HCV)

Other factors exist that are not present in the classical requirements, but which might also be a contraindication for heart donation, such as septicaemia and extra-cerebral systemic neoplasia (Figure 1).

Another factor to consider is donor body surface area, which should not be less than 20% of the recipient's. Given the great dilation of cavities in patients who undergo a transplant, it is unusual for an organ not to fit the chest cavity and impede sternum closure (this occurs more frequently in paediatric patients). An unusually large recipient may require use of a longer upper vena cava, or even occasionally a brachiocephalic vein to ensure correct intercaval distance.

In patients with pulmonary hypertension (PHT) in particular, donor size should not be underestimated since it significantly increases the risk of postoperative right ventricular failure [12,13].

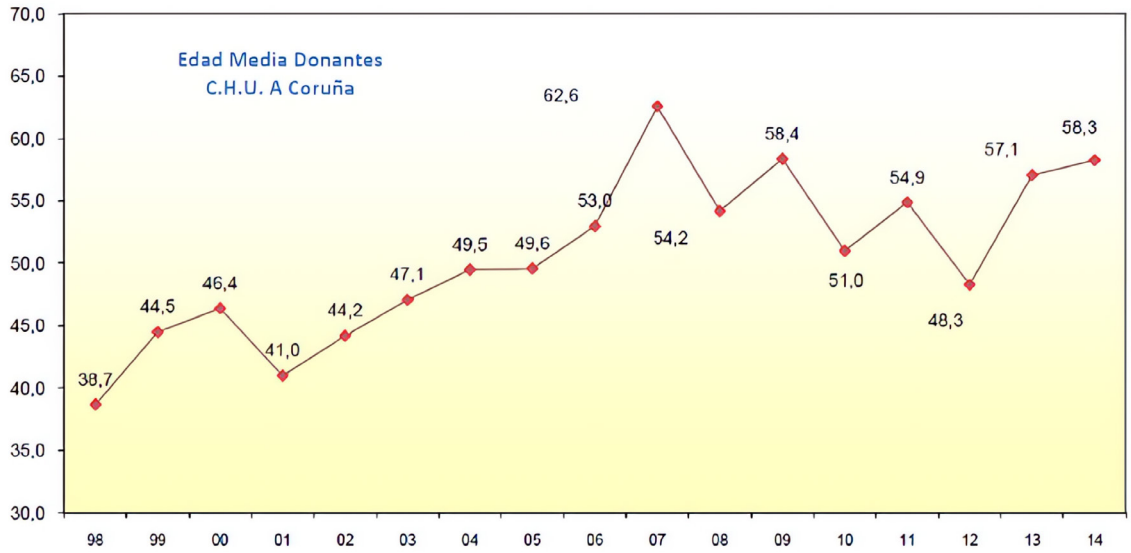


Figure 1. Mean Donor Age in standard centre 1998-2014.

1.1 Donor optimization

Management of a patient who will undergo a multi-organ extraction is frequently a difficult task due to the serious metabolic stress a deceased donor patient is subject to, i.e., the major heat loss of a patient in this situation, often prolonged by co-ordination between the different extraction groups. On occasion, certain manoeuvres that are beneficial for one organ are bad for another, so extreme care is required with intraoperative handling [1,5].

The most common complications (Figure 2) in brain-death (BD) situations are: hypotension, hypothermia and central diabetes insipidus (CDI), which also aggravate haemodynamic instability and electrolytic alterations [9].

It is known that during brain herniation, and in response to the increase in intracranial pressure, brainstem ischaemia occurs, which triggers a massive release of catecholamines. This release causes an increase in vascular systemic resistances (VSR), a rise in arterial pressure (AP) and vasoconstriction that compromises blood flow to the different organs [9,10].

After the sympathetic storm, a normo- or hypotensive phase occurs. Once brain death is established, the ischaemia-necrosis of neurological, brainstem and hypothalamus-pituitary gland structures cause a series of alterations secondary to the absence of brain function as the great "regulating organ". The most common alterations and complications of brain death are:

- absence of spontaneous breathing;
- haemodynamic instability with hypotension;
- loss of body temperature control with progressive hypothermia;
- loss of hydroelectrolytic balance with CDI;
- alterations in hormonal secretion.

Exceptionally, arterial hypertension may appear and when this happens it is generally immediately after brain herniation. It should only be treated if it maintains the following values: PAS >160 mmHg and/or PAM >90 mmHg over time. Treatment should only be with short to medium life drugs because this period is frequently limited and is followed by hypotension. Recommended drugs are sodium nitroprusside, esmolol or Elgadil®.

Arterial hypotension is one of the most common complications that appears in BD. Achieving haemodynamic stability, which guarantees optimum organ perfusion, is a priority goal in donor maintenance. Hypovolemia is one of the basic causes of arterial hypotension; therefore, the first step in treating haemodynamic instability is correct volume replacement with control of CVP. To decide the volume and type of liquids to administer diuresis, ionogram and urinary electrolytic losses must be considered. We recommend avoiding unnecessary transfusions since adverse events may occur, particularly at pulmonary level.

Plasmatic volume expansion should be performed with strictly controlled CVP or pulmonary wedge pressure (PWP) since an excessive speed or volume of liquids administered may cause hepatic congestion and oxygenation deterioration due to hydric overload and acute lung oedema.

We recommend maintaining CVP at 6-10 mmHg and PWP at 8-12 mmHg. For lung donors, a lower CVP (<8 mmHg) is preferred to prevent deterioration of lung function due to hydric overload. If the donor continues with arterial hypotension despite the administration of a correct volume (with CVP at 6-10 mmHg and/or PWP at 8-12 mmHg), it is necessary to start a vasoactive drug. Currently, the most commonly used drugs are dopamine and noradrenaline. Regarding inotropic or vasodilator support, it is important to note the need for inotropic support for low cardiac output or vasodilators due to serious vasoconstriction which occurs in these patients. Some studies report that use of noradrenaline in a heart donor does not affect early survival of patients [1,5,9,10].

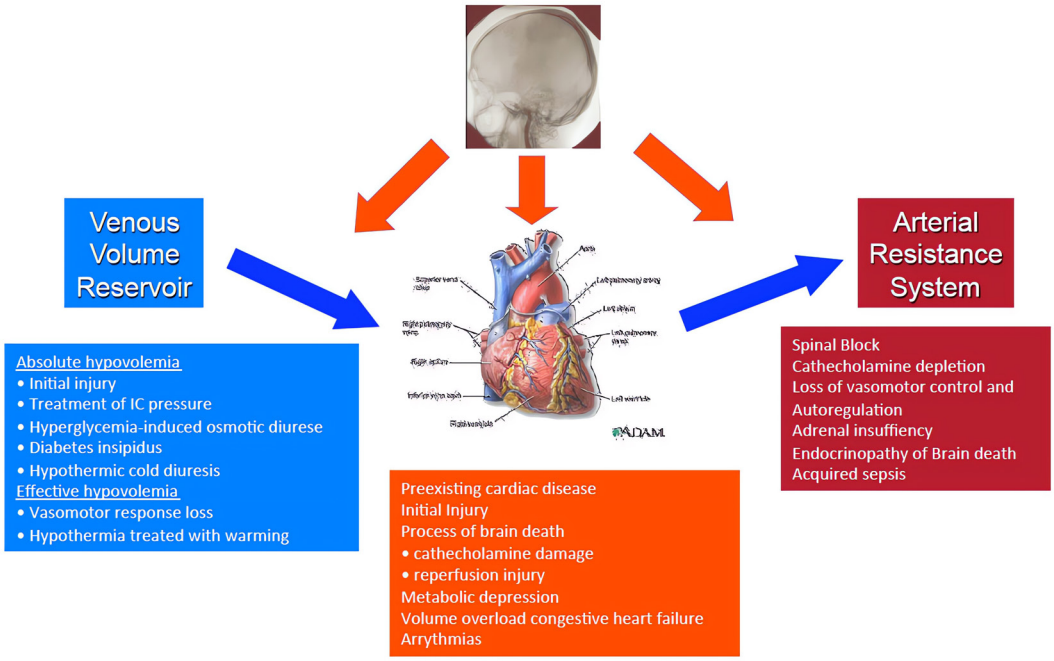


Figure 2. Donor management.

1.2 Harvesting technique

The approach in a heart extraction is via conventional medial sternotomy and pericardial opening for correct heart exposure. In general terms, there are several points to consider for a successful heart harvesting that will provide a good organ for subsequent implant:

» organ validity;

» sufficiently wide margins for anastomosis;

» good myocardial protection.

To verify organ validity, once the clinical history has been reviewed, an echocardiogram is followed by the direct macroscopic evaluation of the organ.

The accepted macroscopic cardiac viability criteria are as follows [10]:

» haemopericardial absence;

» normal contractility;

» atheroma absence in the coronaries;

» absence of cardiac dilation;

There is controversy regarding the palpation of the coronary arteries because calcification of these arteries does not always correspond to significant intracoronary lesion.

For good myocardial protection we must bear in mind the correct use of cardioplegia. There are specially prepared solutions for short-term storage which ensure good results even after 4 hours, although exceeding that limit is not advisable. If we meet these conditions, a total ischaemia of 6 hours maximum can be tolerated. Ischaemia times exceeding 6 hours are associated with primary graft failure. Although publications exist that report successful transplants with an ischaemia time in excess of 9 hours, exceeding the 6-hour limit is not recommended [13].

Another essential consideration for good myocardial protection is decompression of both left and right cavities. This can be performed from different approaches, depending above all on the existence of lung extraction during a multiorgan extraction.

Finally, for correct myocardial protection, the organ must be transported cold with the aim of maintaining its temperature between 4 and 10°C. For the use of other donors, when ischaemia is expected to be long, transport systems enabling hot perfusion of the organ are starting to be used, although this is limited due to transport logistics and the greater expense involved.

Communication with the implant team is of paramount importance during heart extraction for the correct co-ordination of surgical times. This is particularly important when the recipient is a reoperated patient. You must communicate organ validity, aortic clamping time in the donor and departure time from the place of extraction with an approximate calculation of the arrival time at the hospital where implantation is to be performed.

There are two techniques for heart harvesting depending on the existence or otherwise of lung harvesting during a multi-organ procedure.

Heart harvesting starts with wide dissection of the ascending aorta, which can be surrounded by tape if wished. The upper vena cava is dissected from its auricle entry to the brachiocephalic vein. Lastly, dissection of the lower vena cava is performed, opening the pericardial reflection at diaphragm height.

A purse-string suture is placed on the ascending aorta where the cannula will be inserted to infuse cardioplegia. In the event of lung extraction, place another suture on the pulmonary artery trunk (at the level of the bifurcation) to insert cannula for pneumoplegia infusion.

On completion of these steps, you are ready to commence heart harvesting. Sodium heparin is administered at a dose of 3 mg/kg/weight. Next, insert the cardioplegia cannula in the ascending aorta, fixing it to the tourniquet, and once air has been eliminated attach the cardioplegia infusion system. Proceed in the same manner with the pneumoplegia cannula.

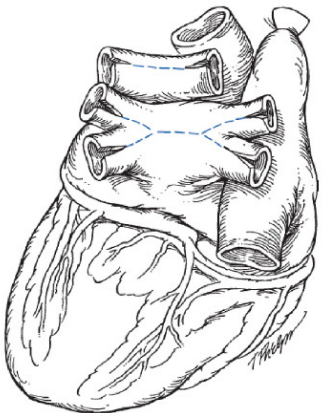
Next, clamp the ascending aorta, start cardioplegia infusion and drain the cavities. To drain the left cavity there are several options: a cut made at upper right pulmonary vein level (provided there is no lung procedure) or over the left atrial appendage, or base of left auricle in the event of harvesting with lung. To drain the right cavity, make a cut at lower vena cava level at diaphragm level. At this point, while administering cardioplegia, pour frozen saline into the pericardial cavity. Check the organ is cooling uniformly and it remains non-distended throughout the whole cardioplegia time. On termination of cardioplegia solution, having checked that the organ has correctly stopped and is well-drained at all times, the aortic clamp can be removed, and heart retrieval performed.

Start by completing the lower vena cava section. At this point, it is important not to approach the coronary sinus to closely nor perform a very wide dissection towards the diaphragm. This is so that the suprahepatic stump is sufficient to perform a liver transplant (approximately 5 mm form the cavoatrial junction).

Next, continue with the section of the pulmonary veins. Should simultaneous lung extraction be performed, extend the incision on Sondergaard's groove to the lower pulmonary veins always leaving a 1 cm round section of auricle surrounding the pulmonary veins so that a lung transplant can be performed (Figure 3).

The upper vena cava is sectioned above the azygos vein, and in some cases - depending on recipient type - use of the brachiocephalic vein may be necessary. The aorta may be sectioned below the supra-aortic vein, or the supra-aortic trunks and aortic arc may be included. The pulmonary artery is sectioned on the pulmonary trunk or both branches separately, bearing in mind that in lung harvesting it is performed below the bifurcation leaving left and right pulmonary arteries intact for lung implant. Finally, complete the section of the left atrial cuff. On completion of heart retrieval, place the organ in a sterile container with cold cardioplegic solution for transportation.

Organ preparation:



Preparation is possible in the place of extraction or on arrival at place of implantation. Prepare the left auricle connecting the upper and lower pulmonary veins of each side via incision, then make a transversal incision.

Should harvesting have been done with the lung, this technique is unnecessary; however, the left atrial appendage could be closed if this option was chosen for left cavity draining. Now, we also look for the existence of a permeable oval foramen to be closed with one suture if existent. The pulmonary artery is prepared, if sectioned at its branch level, via an incision connecting both branches, separating from the ascending aorta and left auricle roof.

Right auricle preparation will depend on the surgical technique to be performed. If the technique is to be bicaval, the upper vena cava is sectioned at azygos vein level. If using the bi-auricular technique, make an incision from the upper face of the lower vena cava, parallel to the auriculoventricular groove in the direction of the right atrial appendage, ligated to the upper vena

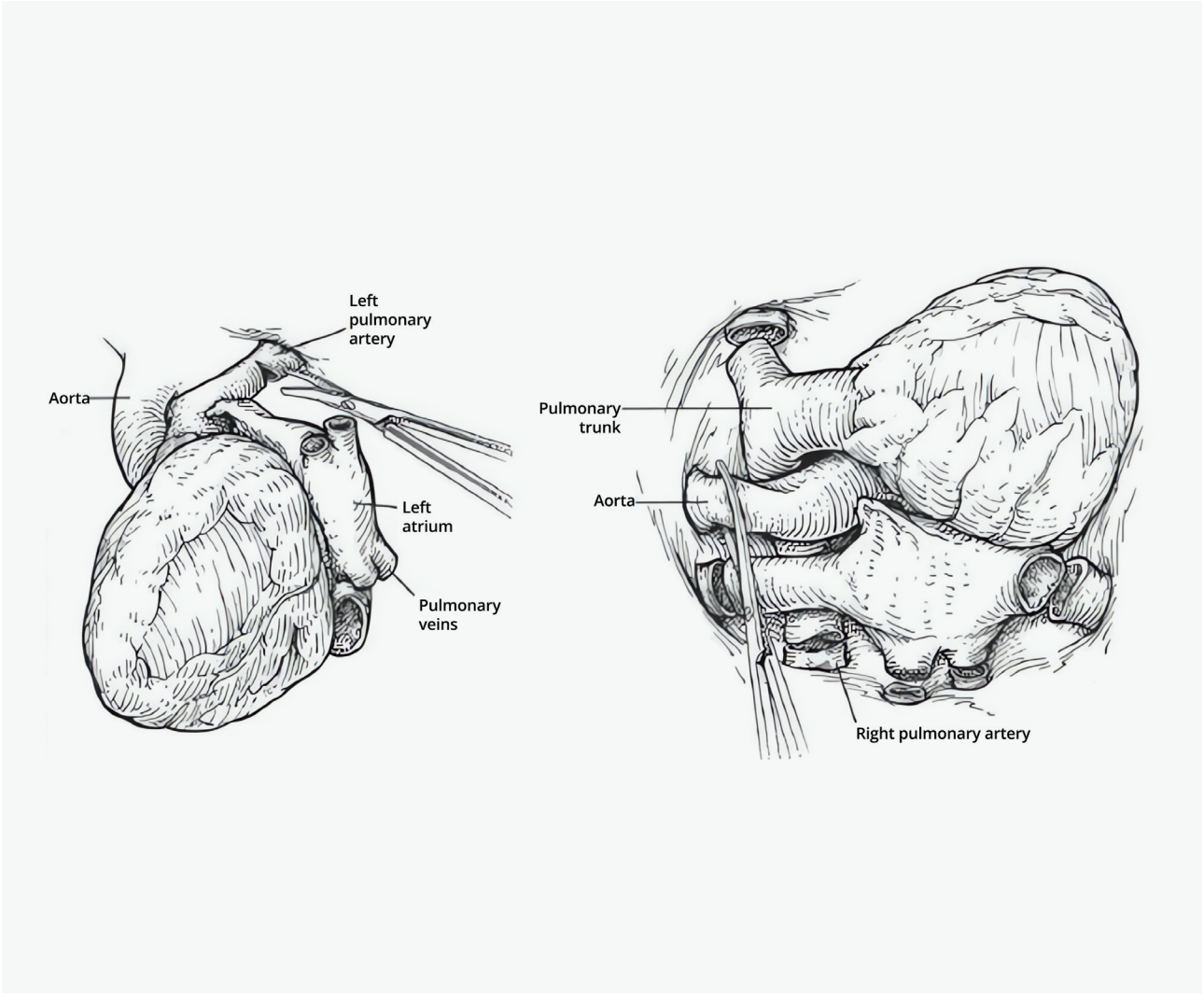


Figure 3. Simultaneous lung extraction.

2. SURGICAL TECHNIQUES FOR IMPLANTATION

2.1 Heterotopic implant

This was the initial technique in experimental HT surgery protocols, but is currently almost never used, although under specific circumstances it may still be indicated. It differs conceptually from the orthotopic implant in that the recipient's heart remains in its natural position and the donor's heart is implanted end-lateral around it.

Thus, its advantage would lie in maintaining original heart function should the donor heart suffer transitory dysfunction (rejection, PHT, donors with prolonged ischaemic storage times, etc.), or should the recipient's heart undergo a potentially reversible process (Figure 4).

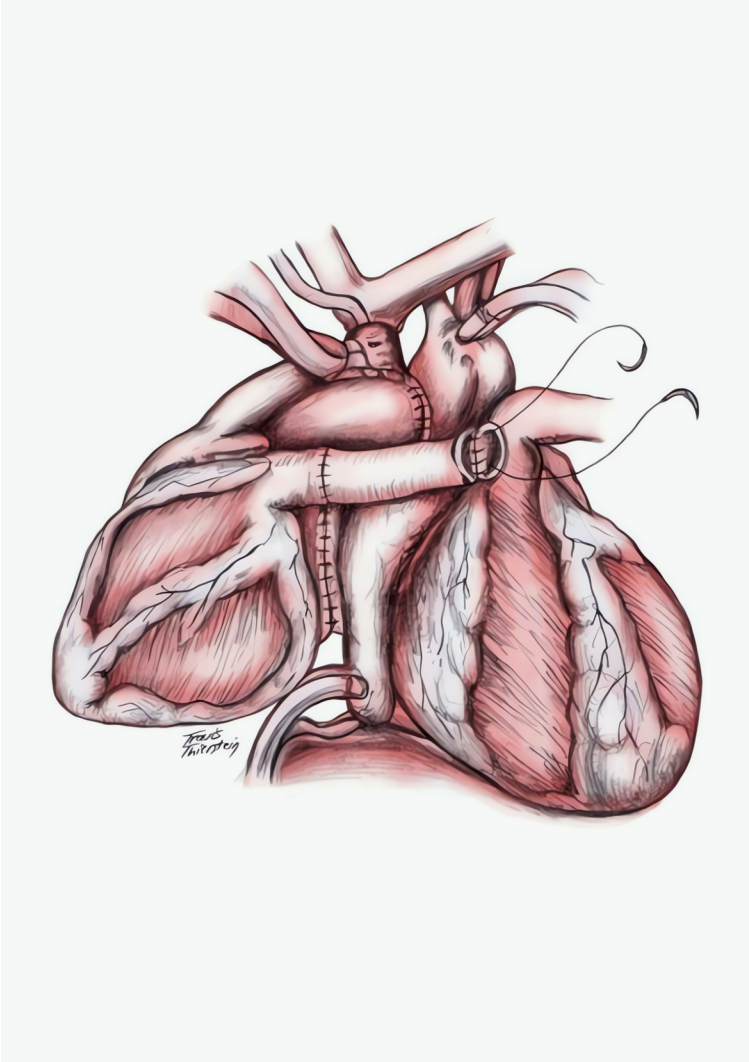
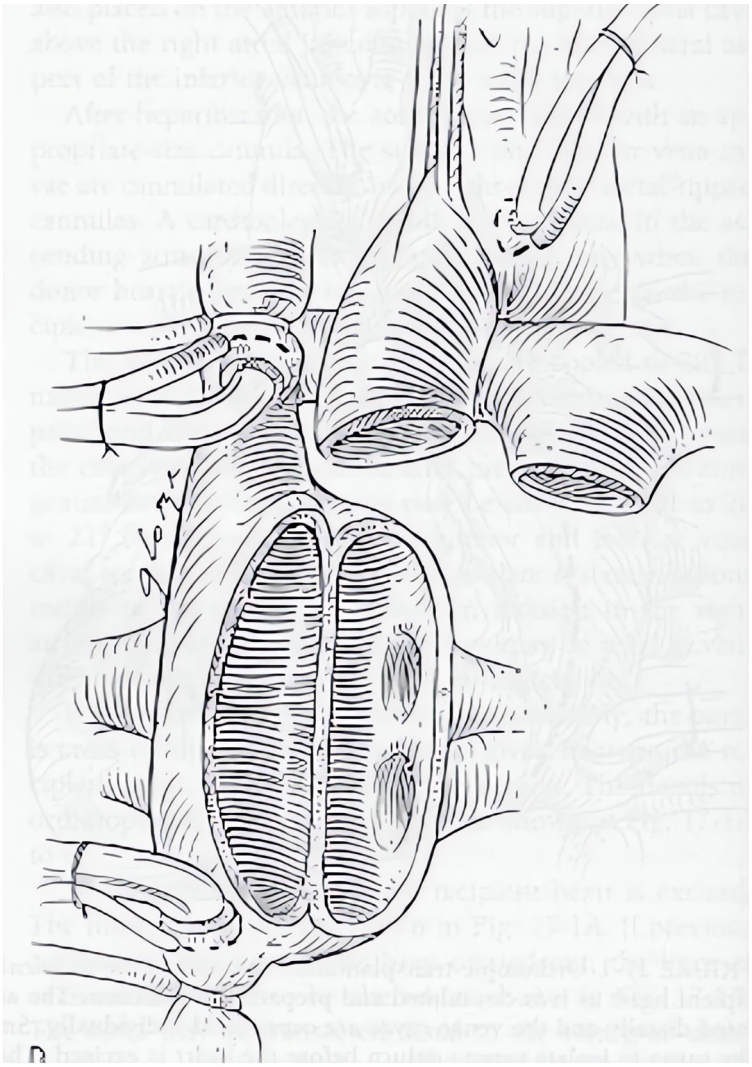


Figure 4. Heterotopic implant.

This technique is more prone to complications than the orthotopic procedure. Donor heart preparation is performed by suturing the right pulmonary veins and lower vena cava. Next, perform anastomosis between the donor left pulmonary veins and a vertical incision on the recipient's left auricle, as in the classical mitral surgery approach. Next, conduct the side-by-side anastomosis between donor and recipient upper vena cava, followed by anastomosis of the donor left pulmonary artery to recipient pulmonary trunk via Dacron tube. The right pulmonary artery is sutured. Finally, perform aorta-aortic anastomosis from the donor descending aorta to recipient ascending. Thus, the donor heart is housed on the right side of the thorax.

2.2 Orthotopic implant



After the original Shumway technique [14], in recent years Reitz et al. introduced the "domino" procedure for thoracic organ transplants. Yacoub (UK) [15] and Dreyfus [16] (France) introduced the "total heart transplant" technique to perfect the transplanted heart's physiology. As an intermediate procedure between the standard and "total" transplant technique, in an attempt to benefit from both, Sarsam and Blanche describe an alternative [17,18], which maintains normal left atrial morphology, leaving the donor right atrium intact. Figure 5 illustrates the three main suture methods.

Figure 5. Orthotopic implant.

2.2.1 Classical technique

Excision of recipient heart

After correct heart exposure, cannulation is performed in the ascending aorta on exit of the brachiocephalic trunk, and drainage of both veins is adjusted by tape after commencement of CPB.

Clamp the recipient aorta and begin an incision from the right atrium to the upper and lower cava, leaving them within an atrial cap. On reaching the septum, incise it and complete another left atrial cap covering the 4 pulmonary veins. The large arteries are sectioned near their origin to leave the maximum in the recipient, as shown in Figure 6.

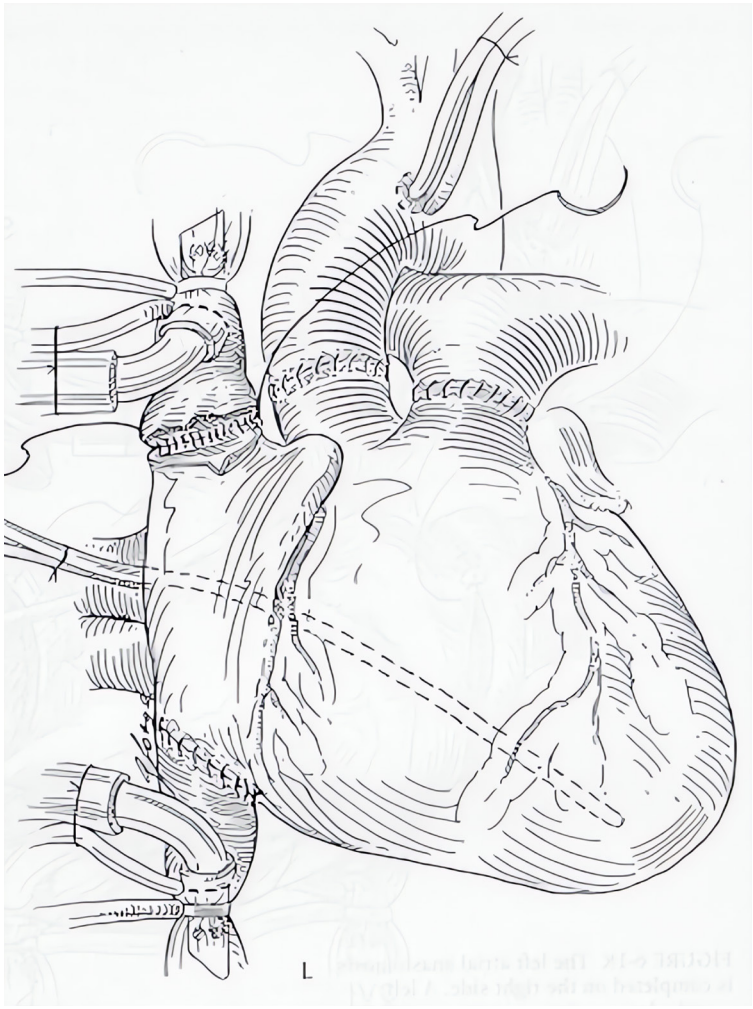


Figure 6. Donor heart implant.

Donor heart implant

Join the 4 entry points of the pulmonary veins in the donor to make a left atrial cap. Ligate-suture the upper cava and open right atrium vertically from the lower cava mouth to the atrial appendage in order to design a right atrial cap.

The implantation starts with anastomosis of the left atrium, usually at the upper left vertex, i.e., from donor left atrial appendage base and recipient upper left pulmonary vein. Suture is completed counterclockwise with non-reabsorbing monofilament. Next, perform anastomosis of the right atrium starting at the upper section of interatrial septum, also counterclockwise.

Both large arteries are sutured in the same way, starting from the left side and suturing from the posterior back wall to the anterior. The pulmonary artery is usually sutured first because it is more posterior and later access with guarantees is more complicated, although if ischaemia time is long, the aorta may be sutured first to enable unclamping and performance of pulmonary anastomosis on a beating heart.

After the completion of implantation, air drainage manoeuvres are performed, and the aorta is unclamped. Different graft protection methods may cause small variations in the order of anastomosis, depending on the preference of the surgical team or to shorten donor ischaemia time. The use and maintenance of cardioplegic solutions during implant might also vary depending on the preservation technic (hypothermia, normothermia, intermittent or continuous, anterograde or retrograde). It would be simpler to sew the heart without any extra cardioplegic dose after removal from the cooler. However, when dealing with longer ischaemia times, the addition of cardioplegic reperfusion doses during implantation seems common sense.

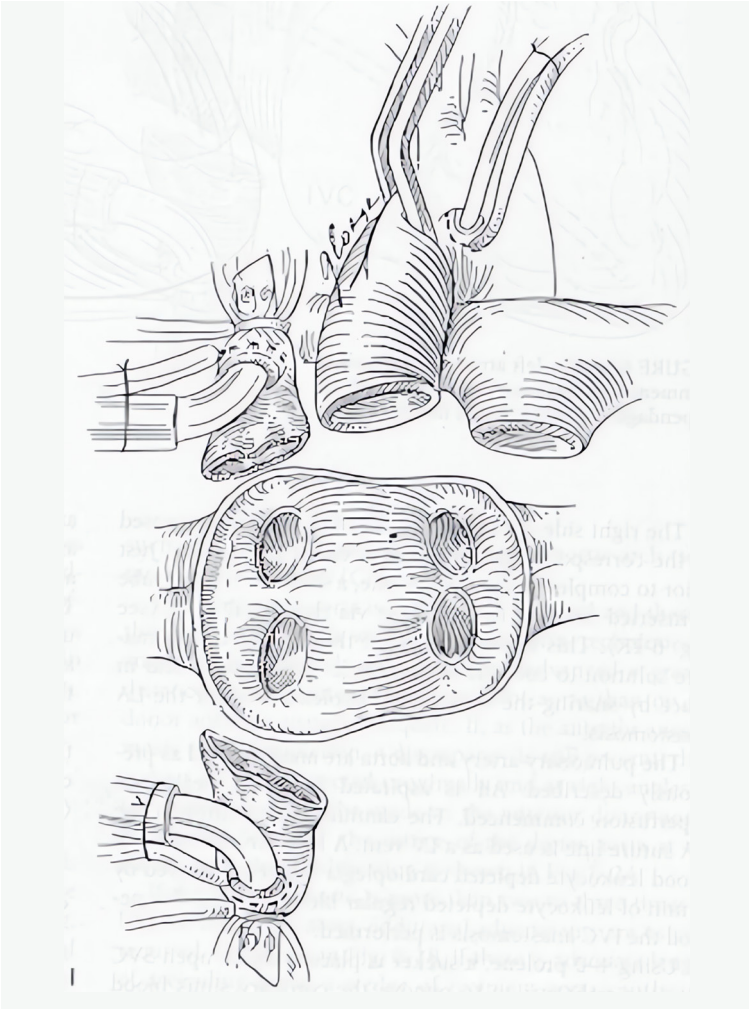


Figure 7. Bicaval technique.

2.2.2 Bicaval technique

Excision of recipient's heart

This differs from the classical technique essentially in its treatment of the right atrium. Incision starts on the interatrial groove, as in a mitral valve approach. The incision continues towards the posterior section of the lower cava and upwards towards the upper cava. Next, section the upper vena cava where it joins the right auricle, continuing the incision of the left auricle to its ceiling below the upper cava direction of the atrial appendage. Next, perform large artery sections in accordance with the classic technique. Complete the left atrial cap cutting. Finally, cut a large cap of the recipient lower cava and extract the part.

Thus, in the pericardial sac we will have a large left atrial cap, a lower vena cava cap (recommended distance between these two caps should not exceed 2 cm), the upper vena cava and large arteries.

Donor heart implantation

Join the entry orifices of the donor pulmonary veins, following the classic technique. The upper cava is cut at the height of the azygos vein. Make an incision of 1-2 cm on the lower cava orifice in the direction of the right atrial appendage to give greater amplitude to this anastomosis. Large arteries are sectioned following the usual technique.

Suture the left atrium with a stitch between the base of the donor atrial appendage and the left upper pulmonary vein. Place another reference-traction stitch between area closest to recipient and donor's lower cava, which ensures the suture has no tension on this stitch besides aiding execution of anastomosis. Non-reabsorbing monofilament 3/0 is used for continuous suture with longer than standard length. The suture is completed counterclockwise, and a vent may or may not be placed on the left ventricle prior to knotting, depending on left venous return.

Next, perform anastomosis of the inferior vena cava with the recipient's one. The suture starts on the left edge of both, continues on the back and finishes on the anterior side.

Next, suture the superior vena cava and aorta end to end, using the same technique as previously. Air drainage manoeuvres are performed in the usual way. As before, if ischaemia time is long, pulmonary trunk and upper vena cava anastomosis may be left until after unclamping (Figure 7).

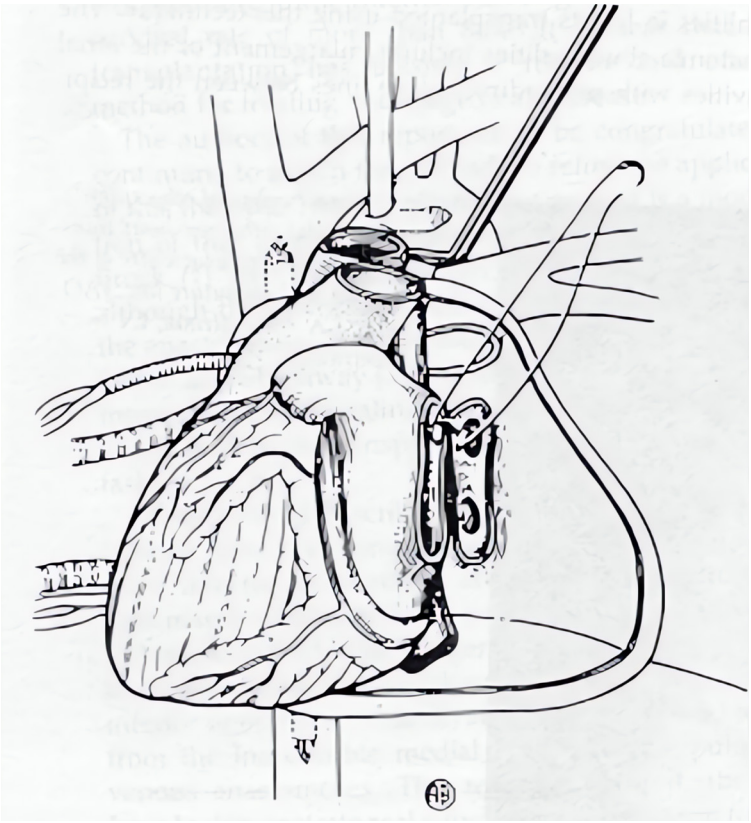


Figure 8. Donor heart implant.

2.2.3 "Total" transplant

This is performed in the same way as the bicaval excision, except that at the end, the left atrial cap is divided into 2 bars, leaving the pulmonary veins on each side sutured separately from the donor heart. Again, it is of particular importance to leave sufficient auricular tissue in the cap of the right pulmonary veins to reach the lower vena cava with the subsequent manoeuvre. The cardiac implant will really be a whole heart with both whole atria.

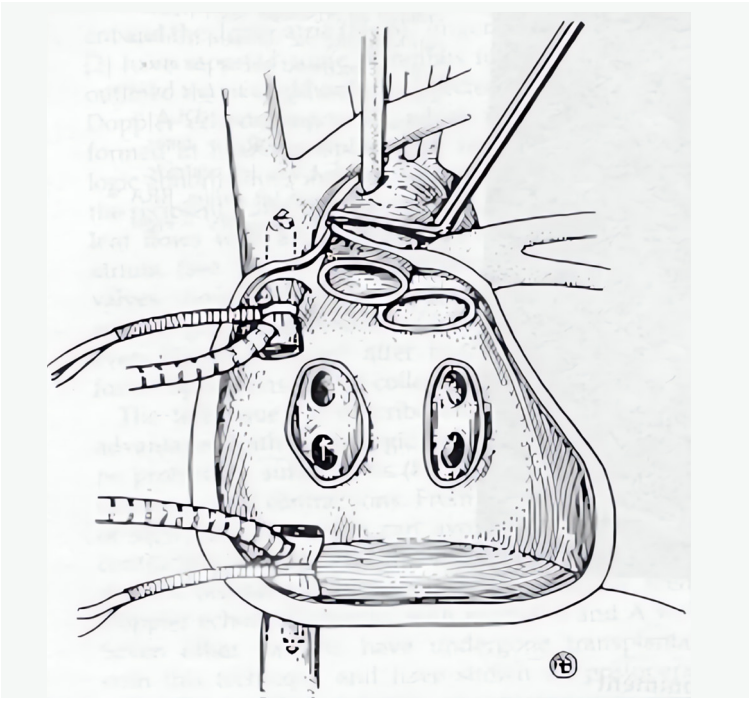


Figure 9. Recipient heart excision.

There are two methods of how to perform this. Yacoub originally described the technique starting with the suture of the left pulmonary veins, with the heart placed on the right side of the surgical fields. Our group opted to perform the 2 sutures of the pulmonary veins with the heart on the left side of the pericardial sac. First, the left veins are sutured, starting from the top and performing the posterior suture to finish counterclockwise.

Immediately after, suture the right veins in the same way. Next, continue with the inferior vena cava, followed by the superior and finally the large arteries as previously described.

In practice, this implant technique does not appear to provide the left atrium with better functionality if care is taken in the bicaval technique to not leave the left auricle excessively large, i.e., caps are cut well before suture. Nevertheless, a bleeding point in the central area of the pulmonary vein anastomosis is difficult to control (Table 1).

Table 1. Advantages and disadvantages of biatrial and bicaval techniques.

	Biatrial	Bicaval
Advantages	» Fastest » Less dissection in reinterventions	» Anatomically better » Less incidence of arrhythmias » Less incidence or tricuspid regurgitation » Less risk of IVC twist
Disadvantages	» Distortion of atrial geometry » Higher risk of arrhythmias » Higher incidence of tricuspid regurgitation » Higher incidence of PPM	» Requires an additional anastomosis

2.3 Special situations

A great advantage of orthotopic techniques is they can be used in combination with reconstructive procedures for anatomical atrial abnormalities, anomalous vena cava or large arteries. This is of considerable interest in a transplant context with recipients who have complex congenital abnormalities, particularly when the patient has undergone previous surgeries.

Many of the techniques generated derive from the complexity of congenital heart conditions and diseases, a description of which is not the subject of this chapter. However, in-depth knowledge of the main techniques described would clearly lead to greater security in the use of more specific manoeuvres.

In any event, the transplant circumstance from a *situs solitus* organ donor to a *situs inversus* recipient is not infrequent in congenital heart conditions. In this case, the left atrium suture should be adapted to place the heart as close as possible the vena cava plane. Ideally the donor organ will arrive with a permeable brachiocephalic vein trunk so the decision will be whether to pass the aorta in front or behind for anastomosis with the upper cava crossing the mediastinum. The back route is shorter but has a greater risk of compression. The inferior cava anastomosis is even more complicated, requiring flaps to be created from leftover recipient tissue and may even require reinforced PTFE synthetic tubes.

Given its particular frequency, this section is dedicated to aorta reconstruction. Atrial sutures adapt relatively easily, as does the pulmonary artery; however, in the aorta, a disparity in size between donor and recipient can be very large.

In the event of a moderate disproportion, a longitudinal incision of only approximately 1 cm on donor aorta is required, then suturing can continue in the usual way. Should there be a large disproportion a more complex repair may be required.

Perhaps the aspect that has most decisively contributed to HT becoming a first-tier therapeutic option is the straightforwardness and safety of its surgical technique in its classic description. Given this circumstance, any technical modification that implies greater complexity or a reduction in safety should be considered unnecessary unless an extremely solid basis exists. In this context, many authors consider the introduction of modifications that tend towards "total heart transplant" as a technical ostentation, which complicates the intervention making it less safe. Moreover, such modifications provide no clinical benefit for the patient. The findings of transthoracic, and more recently with their greater definition and scope, transoesophageal echocardiograms show that the conventional orthotopic heart transplant does not normalize anatomical auricular configuration, altering its physiology [19-21].

Among the anatomical anomalies described in literature at auricular level are increased auricular areas, side suture prominence offering the typical "hourglass" configuration, pseudo-aneurismatic formations in the interauricular wall, heart rhythm alterations due to conduction system lesion, and asynchronic auricular contraction. However, perhaps the finding with greatest clinical repercussion is the presence of intracavity clots [22,23].

In the light of such findings, perhaps we should consider alternative surgical techniques that preserve auricular anatomy and therefore normalize its physiology. Regarding the technical variations previously considered, bicaval anastomosis is the most straightforward and safest as all of the sutures are accessible for the addition of complementary stitches if necessary. Furthermore, it can still be used when the heart and both lungs are extracted for 3 different implants, since it requires less left donor auricle than the total heart transplant technique.

The myocardial protection methods used by the different surgical teams are as varied as the surgical technique itself. By way of example, the most straightforward technique involves implantation of the donor heart as it leaves the cooler box without cardioplegic maintenance solutions or reperfusion, with performance of the left atrial suture followed by the aorta, for unclamping and suturing of the others with a beating heart. The most complex techniques involve the use of continuous anterograde normothermic blood cardioplegia throughout the implant, or intermittent cold blood cardioplegia. Thus, we see that it is possible to alter the order of anastomosis depending on the specific strategy [24].

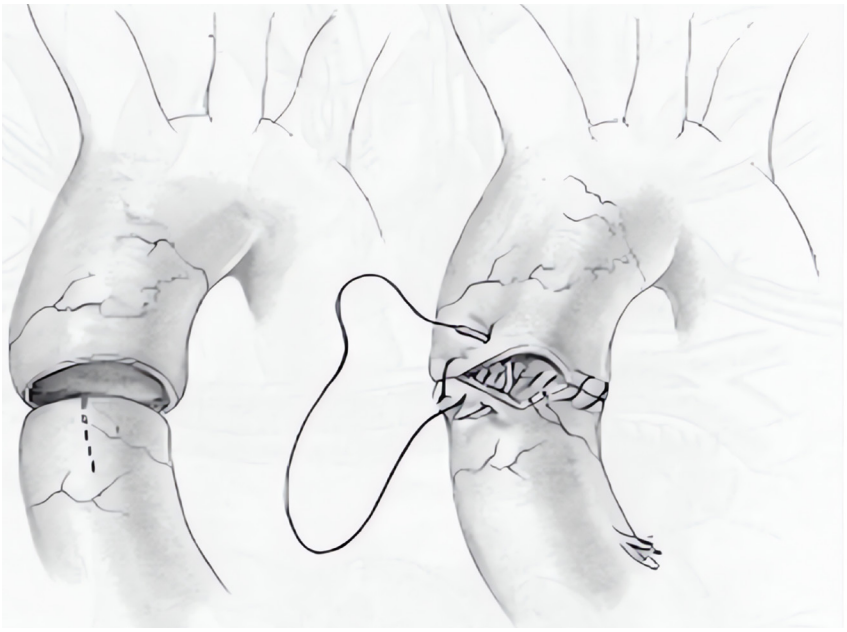


Figure 10. Aorta reconstruction.

3. EARLY POSTOPERATIVE COMPLICATIONS

These occur during the first postoperative month, are frequent during the immediate postoperative period, and may be related to the surgery, high immunosuppression levels or graft failure.

3.1 Premature graft failure

Defined as a reduction in graft contractile function, its incidence is estimated at approximately 10% of cases, and it is the first cause of mortality during the first month posttransplant. Among the different causes it is related to are:

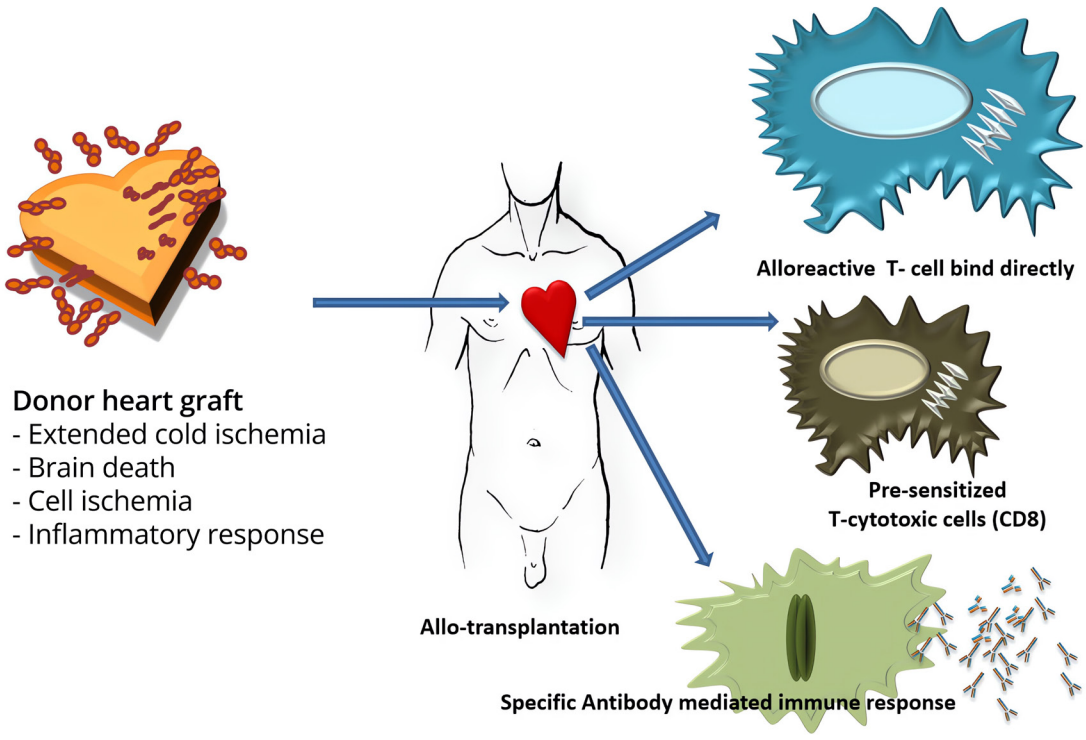
Primary graft failure

There is significant graft contractile disfunction from the beginning of the postimplant phase. It is secondary to traumatic, metabolic and/or haemodynamic donor heart damage before explantation and related to bad graft preservation or existence of prolonged hot or cold ischaemia periods [25].

Hyperacute rejection

This is an immunological reaction of the recipient to the graft due to preformed antibodies against HLA epitopes or donor ABO system antigens. It is observed minutes or hours posttransplant with the myocardium becoming oedematous and haemorrhagic leading to irreversible graft loss.

Treatment consists of plasmapheresis to attempt to eliminate the donor-preformed antibodies and the use of antilymphocyte agents like OKT-3 or cyclophosphamide. Prognosis is bad, and we should consider implanting a ventricular assist device and urgent retransplantation. Given the current shortage of donors, a series of heart transplants in incompatible ABO systems with good short- and long-term donor results have been published [26].



Technical surgical problems

As mentioned in the previous unit, the most widely used technique for graft implant is the bicaval. Apart from the technical problems of any heart surgery like re-entry in a patient with previous surgeries, cannulation problems, air embolism, bleeding, etc., there are some problems specific to heart transplant surgery. Probably the most common technical problem is pulmonary artery torsion, particularly in re-intervened patients with prior adherences. Torsion generates obstruction of the right ventricle exit, which may cause acute ventricular failure. To prevent this, the donor pulmonary artery should be cut back as much as possible.

On exiting CPB, direct pressure measurement in the right ventricle and the pulmonary artery distal to anastomosis enables the definition of these symptoms and a differential diagnosis with right failure due to PHT. In the bicaval technique, anastomosis between the donor superior vena cava and that of the recipient is also complex and may result in stenosis. To minimize this risk, we recommend anastomosis with monofilament 5/0 block continuous suture every 2-3 stitches to prevent a purse-string effect and knot suture. With aortic anastomosis, formation of pseudoaneurysms has been described exceptionally. Verified aortic pseudoaneurysm is a reoperation criterion [27].

A special situation which is becoming more frequent is patients who must be transplanted after implantation of a medium-long term ventricular assist device. To prevent problems with resternotomy and facilitate aorta-aortic anastomosis, some authors recommend femoral cannulation, likewise amputation of the left ventricle apex in the cardiectomy and leaving system extraction for once implant is performed, while the heart reheats leaving CPB [28].

There are also special circumstances in congenital cardiopathies that require technical modifications like heterotaxy, *situs inversus* arrangement, and congenitally corrected transposition of the large arteries where the aorta is on the left and pulmonary artery on the right. The first two have been described in detail [29]. In the latter circumstance, we usually avoid anastomosis in "X" on large vessels, recommend conducting the aorta anastomosis as standard and performing anastomosis of the donor pulmonary artery to the recipient right pulmonary branch prior to closure of the pulmonary artery trunk.

In patients with a univentricular physiology who have been undergone total pulmonary cavopulmonary anastomosis (Fontan operation), we must bear in mind that the anastomoses of the cava will be more complex. In the case of superior cavopulmonary anastomosis (Glenn surgery), the superior vena cava must be disconnected from the right pulmonary artery, on which repair is subsequently performed with a pericardial patch.

Afterwards, it is usually directly anastomosed to the donor superior vena cava. However, the lower vena cava usually needs to maintain part of the Gore-Tex which the inferior cavopulmonary anastomosis formed (Fontan surgery) and perform anastomosis between this and the donor inferior vena cava. In these patients, it is not infrequent to have a left superior vena cava anastomosed to the left pulmonary artery, which usually reaches the right atrial appendage via an appropriately sized Gore-Tex tube. Whenever we face a transplant on a congenital heart condition it is important to rule out the existence of a patent ductus arteriosus or stenosis of any pulmonary vein. The current recommendation is for transplants on complex congenital heart conditions to be performed by teams with experience in these patients.

Pulmonary hypertension

The increase in pulmonary vascular pressures and resistances is a common physiopathological situation in terminal heart failure patients, subsidiary to heart transplant. Left ventricle dysfunction in many cases conditions a retrograde increase in pulmonary pressures which is initially reactive, partly due to vasoconstrictor stimuli on the middle layer of pulmonary vasculature. Chronically maintained, such stimuli cause hypertrophy of the middle layer, fibrosis of the intima layer and consequent permanent pulmonary vascular damage. In patients selected for heart transplant these elevated resistances usually become normalized posttransplant, although it may take weeks or months to return to correct values.

In summary, an average transpulmonary gradient over 12 mmHg and/or pulmonary vascular resistance over 2.5 WU are associated with premature morbidity and mortality posttransplant, essentially due to right ventricular dysfunction [25]. Transpulmonary gradient values over 15 mmHg or a pulmonary vascular resistance over 6-8 WU contraindicate transplant, as the right ventricle is particularly susceptible to ischaemia and reperfusion periods and may present adaptation failure due to acute increase of afterload. Post-implant right ventricle failure treatment requires preload optimization, inotropic support, and systemic and pulmonary vasodilation. Should these measures be ineffective, a ventricular assist device should be considered.

Patients with complex congenital heart conditions which have been alleviated following a univentricular option experience chronic cyanosis and the absence of a ventricle that ejects pulsating blood to pulmonary circulation, which conditions chronic abnormalities in their pulmonary vasculature. Moreover, general or localized pulmonary artery development problems are common in these patients. However, the absence of pulsating pulmonary flow means that the pulmonary pressures and resistances obtained in the pretransplant haemodynamic study are usually within a "normal" range. The onset of right ventricle failure in this specific patient group is extremely frequent and should be ruled out before the presence of any haemodynamic instability during the immediate postoperative period. Medical treatment for this population is generally poorly efficient so early mechanical ventricular assistance should be started. The difficulty of these patients is due to complexities that are preoperative (cyanosis, kidney and liver failure, presence of multiple antibodies against recipient), intraoperative (3rd or 4th reoperation, the need for pulmonary repair, disconnection and reimplant of previous cavopulmonary anastomosis) and postoperative. This means that patients with a univentricular physiology should always be evaluated and transplanted by a group with experience in congenital heart conditions.

Acute cellular, humoral or mixed rejection

Acute cellular rejection may occur between days 3-4 posttransplant; however, given the more aggressive immunosuppression protocols during week 1, it usually occurs in weeks 2-3, when immunosuppression is undergoing adjustment. It is characteristic in young patients, women with autoimmune or inflammatory cardiomyopathy, or patients with suboptimal immunosuppression levels, which are usually related to kidney failure or concomitant infection. Acute humoral rejection may even be more premature than cellular rejection and has a worse prognosis. It typically occurs in "sensitized" patients, like multipara women, patients who have received transfusions or previously undergone surgery with vascular homografts.

Haemodynamically, patients with acute rejection present signs of low cardiac output, restrictive ventricular filling pattern and arrhythmias. In both cases, diagnosis is via endomyocardial biopsy, with which we can observe infiltration by neutrophils and macrophages (cellular), IgM or IgG antibodies or immunocomplexes (humoral) or both (mixed). Acute rejection will be dealt with in greater detail below.

3.2 Infection

There are 3 infection types in the immunocompromised patient:

1. secondary to real pathogens;
2. produced by occasional organisms;
3. due to opportunist pathogens.

The pathogen that infects heart transplant patients with greatest clinical importance is cytomegalovirus. The most common micro-organisms isolated in infections occurring in the immediate postoperative period are staphylococcus and gram-negative bacteria, the most common being pneumonia, bacteraemia/sepsis due to intravascular catheters and surgical wound [25].

Infections in the transplanted patient are detailed in another section. The use of perioperative antibiotics and early removal of vascular catheters may reduce the incidence of these infections.

3.3 Arrhythmias

Rhythm disorders are highly frequent immediately post-operation. Supraventricular tachyarrhythmias (fibrillation and flutter) are frequently and usually related to vasoactive drugs. However, they are also linked to the creation of re-entry circuits during surgery. Presence of tachycardia or ventricular fibrillation should make the existence of graft dysfunction suspect.

Graft sinusal dysfunction constitutes a very frequent arrhythmia in the immediate postoperative period after a heart transplant, affecting over 40% of patients depending on the series. This arrhythmia is present as a sinus bradycardia, rhythm of union or sinusal pauses. In most cases, spontaneous recovery occurs in the first three weeks posttransplant. Treatment consists of prophylactic administration of isoproterenol or isoprenaline, which is a β adrenoceptor agonist that produces vasodilation and positive chronotropism, with the majority of groups administering it from the operating theatre. Heart stimulation can also be used with a temporary pacemaker, and should the disorder continue, with a definitive pacemaker, although this occurs in less than 5% of patients [27].

Complete atrioventricular block is much less frequent (6%), and onset is generally late. This onset has been related to the existence of an underlying rejection process, so for *de novo* development of the arrhythmia, an endomyocardial biopsy is recommended.

3.4 Respiratory failure

There are number of reasons for respiratory failure post-heart transplant, the most outstanding of which are acute pulmonary oedema due to graft dysfunction (cardiogenic), immunosuppression therapy, or associated lung infections (non-cardiogenic).

Chronic treatment pretransplant with amiodarone has also been related to post-surgical respiratory failure.

3.5 Acute renal failure

The aetiology of posttransplant kidney failure is also multifactorial and includes low peri-operative cardiac output, CPB, presence of associated comorbidities like diabetes and immunosuppressive therapy.

In this context, the use of induction therapy with monoclonal antibodies (basiliximab) guarantees an initial intense immunosuppression that enables the establishment of more gradual support treatment with calcineurin inhibitors. In some cases, particularly when there is a history of renal dysfunction, early commencement of hemofiltration or even definitive dialysis is necessary.

3.6 Haemorrhage

Patients subjected to a heart transplant usually have a high risk of haemorrhage due to pretransplant therapy which usually includes anticoagulant and/or antiplatelet drugs. The urgency of the transplant itself impedes suspension of these drugs within a reasonable period of hours or days. Furthermore, approximately 30% of patients have usually undergone previous surgeries.

Due to this and other associated comorbidity factors, these patients frequently experience haemorrhage, which makes haemorrhage control strategies important since an uncontrolled clotting disorder may lead to a bad result for a good heart graft.

In general, we must:

- Monitor drainage meticulously.
- Rewarm the patient, controlling haemodynamic signs and agitation.
- Anticipate major significant bleeding and replace blood component deficits particularly if dysfunctions are suspected, even before receiving the results of tests.
- As soon as analysis results arrive, therapy must be readjusted more specifically. Generally:
  - An increase in PT implies administration of clotting factors.
  - An increase of PTT or ACT may be due to a residual heparin effect and thus add more protamine; although this is not always the case, and excessive protamine may have anticoagulating effect.
  - Maintain platelets over 100,000.
  - Maintain a correct HCT, preferably over 25-30%.
- Specific agents to consider:
  - Protamine 25-50 mg; if ACT does not decrease do not administer more.
  - Desmopressin as coadjuvant in platelet dysfunction.
  - Calcium chloride must be used, particularly in the case of polytransfusion.
  - Fibrinogen: maintaining figures over 150-200 mg/dL.
- Factor VIIa recombined when a problem is difficult to control. Although probable systemic thrombosis has been described (5-10%), its specific "explosive" action at bleeding point is highly effective.

CONCLUSIONS

» When evaluating a prospective donor, a transthoracic echocardiography is the test which provides us with most information, although we must evaluate the other tests performed and make decisions case by case.

» Traditional criteria for donor consideration may currently be less strict and the possibility of rescuing what is a priori a bad donor with correct management may require consideration.

» Likewise, an optimum donor may fail if the metabolic requirements during the extraction process are not followed.

» The technique for harvesting is straightforward, but good myocardial protection is essential. Ideally the donor heart must stop in optimum conditions, be well discharged and have a specialized cardioplegic solution for prolonged cold ischaemia.

» Good co-ordination between retrieval and implant teams is more important than the techniques themselves. A 30-minute difference in prolonged ischaemia may be very significant.

» • We must learn all implant techniques; however, each team should be clear about the advantages and disadvantages of each technique, adapting to that which gives best results. The bicaval technique offers very good results with little added risk.

» In complex situations, reoperations, and particularly in congenital heart conditions, surgical technique must be thorough, often using alternatives to a standard implantation. One of the most difficult situations is a patient with visceroatrial situs inversus.

» Premature graft failure is the most dreaded complication during the early transplant postoperative period. Its cause must be identified, and treatment must commence as soon as possible to prevent organ loss.

» Currently, the most common surgical technique problems are the arrival of recipients with higher morbidity, reoperative surgeries, or with ventricular assist devices and congenital heart conditions in adults.

» Pre-/post-operative PHT must be identified for aggressive treatment before it causes ventricular failure.

» We must be on high alert during weeks 2 and 3 for possible acute cellular rejection, particularly if there have been changes in or adjustments to immunosuppression.

» Haemorrhage control is crucial since it may lead to deterioration of what is, a priori, a good graft. We should use both haematological contributions and coadjuvant drugs with conviction.

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TOPIC 5 - Unit 3

Postoperative management and medical follow up (early/late and histopathology/radiology)

ORGAN TRANSPLANTATION

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INTRODUCTION

Survival after heart transplant (HT) has improved over the years, and according to the latest international register data, average life expectancy is currently 11 years. Year 1 post-HT is the greatest risk period with mortality around 20%. Among patients who survive the first year, average survival is 14 years. In the Spanish HT register, the most frequent cause of death is premature graft failure (16.5%), followed by infection (15.9%), graft vascular disease (GVD) (13.7%), tumours (11.9%) and acute rejection (7.8%).

On analysing mortality by periods, premature graft failure (also called acute graft failure, AGF) is the main cause of death in the first month post-HT, between month 1 and year 1 the first cause is infections, and from year 1, GVD and tumours are accountable (Figure 1).

When attending HT patient complications and emergencies, the following basic principles apply:

- In the event of emergency, consultation with the HT team responsible for patient follow-up should always be considered.
- Never suspend immunosuppression without prior consultation with the HT team responsible for the patient.
- Particular attention must be paid to the:
    1. possibility of acute and/or chronic rejection; and
    2. complications of chronic immunosuppressant use (toxicity, infection risk and tumours).

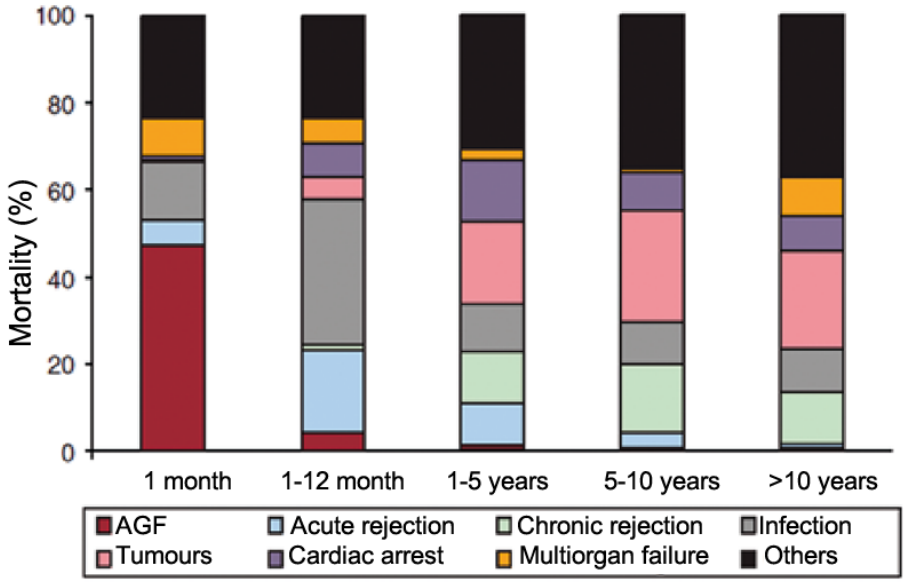

Figure 1. Mortality analysis.

1. IMMUNOSUPPRESSION

The long-term success of HT is based on maintaining an effective suppression of immune response in order to prevent acute and chronic graft rejection, while using the lowest possible dose of immunosuppressive drugs to minimize long-term adverse effects, particularly infections and neoplasms.

Most of the immunosuppression currently in use involves a combination of several agents acting in synergy to enable a reduction in the dose of each drug and therefore of its side effects. The following provides a brief description of the different drugs and systems used in HT immunosuppression as well as their possible adverse effects and interactions.

Induction therapy

The term induction therapy (IT) is used to designate the most intensive degree of immunosuppression used initially post-HT to ensure the deep, rapid suppression of immune response. This therapy reduces the incidence of acute graft rejection and enables later introduction of calcineurin inhibitors (CNI), preventing kidney function deterioration during the initial critical moments of HT. Nevertheless, IT has been associated with a greater risk of infections. After 40 years of HT, the use of IT is still debated since it lacks large clinical trials that prove its superiority in terms of survival compared to the direct commencement of maintenance immunosuppression [1]. In Spain over 80% of HT patients receive IT, with basiliximab (monoclonal antibody anti-CD25), the most commonly used drug.

Maintenance immunosuppression

Maintenance immunosuppression in HT includes 3 basic components: a calcineurin inhibitor (cyclosporine or tacrolimus), an antiproliferative agent (mycophenolate mofetil, MMF) and steroids. The greatest risk of rejection occurs in the first 3-6 months post-HT, thus the aim in this period is to achieve maximum immunosuppression. This risk subsequently drops, and immunosuppression may be progressively reduced, based on biopsy results and individual patient risk. The current trend is to attempt reduction of CNI nephrotoxicity and the metabolic effects of steroids. Nowadays, some systems use proliferation signal inhibitors (PSIs, everolimus and sirolimus) to reduce the dose or eliminate CNI or steroids.

Calcineurin inhibitors (CNI)

Two CNIs are currently used Spain: cyclosporine (CsA) and tacrolimus (Tac).

Their immunosuppressive action is based on inhibiting the genes which code inflammatory cytokine expression, like IL-2, preventing T lymphocyte activation and proliferation. The introduction of CsA in clinical practice marked a significant increase in post-HT survival. Use of the formula in micro-emulsion is associated with a reduction in rejection episodes and requires a lower dose, which is the reason for its current extended use. At the end of the 1990s, Tac was introduced and progressively incorporated as a CNI. Recent studies indicate initial immunosuppression with Tac reduces rejection at six months and one year without survival differences in comparison to CsA [2]. Due to their average life, both are administered every 12 hours. Tac is also available in prolonged liberation for administration once a day, which gives an improvement in adherence, particularly among young patients.

The major limitation of CNI is its adverse effects depending on the drug concentration in blood. The initial CsA dose is 2-3 mg/kg/12 hours and Tac 1-2 mg/12 hours. Dosage and monitorization of drug levels are subsequently adjusted in accordance with each patient's characteristics and the time elapsed since HT in order to minimize toxicity while maintaining therapeutic levels. Table 1 shows the minimum levels (C0) recommended for CNI [3].

Table 1. Lowest target levels for CsA and Tac in association with MMF and steroids

Post-HT period	CsA (ng/ml)	Tac (ng/ml)
Months 1 and 2	200-350	10-20
Months 3 and 4	200-300	10-15
Months 5 and 6	150-250	5-15
Months 7-12	100-250	5-15

Antiproliferative drugs

Azathioprine (AZA) and MMF act by inhibiting the synthesis process of purines, suppressing T and B lymphocyte proliferation. In current immunosuppression protocols, MMF has replaced AZA, the first antiproliferative used in HT, as it has greater immunosuppressive strength and is associated with greater survival and lower rejection during first year of follow-up. Furthermore, the greater power of MMF enables a reduction of CNI dosage in patients with kidney failure without increasing the risk of rejection. It has also been observed that MMF has a protective role against AZA in graft vascular disease (GVD) [4].

The dose of MMF used in treatment is 2-3 g/day divided into 2 doses. Dosage should be adjusted and reduced in the event of an onset of adverse effects, the most common being myelotoxicity (especially leucopoenia) and gastrointestinal intolerance. The usefulness of monitoring mycophenolic acid levels of the MMF active metabolite to control efficacy and adverse effects is still controversial. As a result, its use in treatment is reserved for specific situations such as therapeutic non-compliance, major changes in immunosuppression or relevant clinical events. The pharmacological interactions of MMF are scarce and generally of little relevance. Mycophenolate sodium (MFS) is an enteric coated formula designed for better digestive tolerance of MMF, with an efficacy and safety profile similar to MMF. Equivalent doses are 1,000 mg MMF = 720 mg MFS and 1,500 mg MMF = 1,080 mg MFS.

Steroids

Steroids are a standard in post-HT induction, maintenance and rejection treatment. The usual initial treatment is 3 doses of methylprednisolone 125 mg IV every 8 hours, the first immediately post-HT. Next, with oral prednisone 0.8 mg/kg/day divided into 2 doses during the first week post-HT, then gradually reduced weekly at a rate of 0.2 mg/kg until reaching 0.2 mg/kg/day once a day, which is the maintenance dose until 3-6 months.

Steroid treatment is associated with a wide variety of adverse effects including hypertension (HTN), DM, hyperlipidaemia, osteopenia, delay in wound healing, myopathy and emotional lability, which may imply a worsening quality of life, morbidity or progression of GVD. Therefore, after the first 3-6 months post-HT, most centres try to progressively reduce steroid dosage to a basal minimum or even completely eliminate their use in patients with a low risk of rejection and/or high risk of steroid-related complications. Monitoring of steroid reduction is advisable by means of control endomyocardial biopsies. The presence of graft rejection would force the reintroduction or increased dosage of steroids. According to the ISHLT register, a successful steroid elimination rate at 1- and 5-years post-HT is 20% and 49% respectively [5].

Proliferation signal inhibitors (PSI)

Mammalian target of rapamycin (mTOR) inhibitors, also called PSI (everolimus and sirolimus), work against T and B lymphocyte proliferation, likewise smooth muscle cells, and have opened up new expectations for HT immunosuppression. In comparison with azathioprine, PSI treatment has been associated with a reduction in acute rejection episodes in patients treated with CsA and steroids. Likewise, everolimus and sirolimus have shown a protective role in the development of GVD [6,7] and a potential advantage due to their capacity to mitigate or reduce the progression of neoplasms (appreciated in experimental studies and transplants of other organs) [8-10]. However, to date, it has not been demonstrated that the CNI-PSI association improves survival compared to classic therapy with CNI and antiproliferative drugs [1].

The initial dose of everolimus is 0.75 mg orally every 12 hours, adjusting dose to maintain minimum target levels between 3 and 8 ng/ml. Sirolimus is administered in a single initial daily dose of 2 mg every 4 hours after CNI, subsequently adjusting dosage to reach target levels between 6 and 12 ng/ml. The main adverse effects of PSI include myelotoxicity (especially leucopoenia), dyslipidaemia, oedema, gastrointestinal alterations, delay in healing and interstitial pneumonitis. Furthermore, PSI have been associated with a greater risk of bacterial infections, particularly pneumonia. Therefore, after commencing PSI treatment it is recommended to administer co-trimoxazole for at least one year as Pneumocystis jirovecii (PJP) prophylaxis. Although PSI are not intrinsically kidney toxic, in combination with CNI the nephrotoxic effects increase [11].

Due to their hepatic metabolism via cytochrome P-450, PSI present some pharmacological interactions of note. The most studied association of the PSI-CNI combination is that of CsA and Everolimus. The combined administration of both drugs does not alter the pharmacokinetics of CsA, although it does cause an increase in maximum everolimus concentration, which should be taken into account when modifying or eliminating CsA doses. Other drugs which increase PSI levels are calcium antagonists, macrolides and azole antifungals; however, rifampin, carbamazepine, phenobarbital and phenytoin reduce PSI levels.

Today, PSIs are essentially used as a replacement for MMF in GVD and also as an alternative to CNI, whether as a replacement or combined with lower CNI doses in patients with chronic kidney failure and as anti-neoplastic agents.

Table 2 shows equivalent doses for oral and endovenous intake of the main immunosuppressive drugs used in HT [1].

Table 2. IV dose of main immunosuppressants used in HT

Post-HT	1/3 of administered daily oral dose, either in continuous infusion for 24 hours or divided into 2 daily 6-hour infusions
Tacrolimus	1/5 of administered daily oral dose in continuous infusion for 24 hours
Mycophenolate mofetil	Same as oral dose
Azathioprine	Same as oral dose
Months 7-12	100-250

Other drugs

1. Statins (HMG-CoA reductase inhibitors) are not only lipid-lowering medication but also immunomodulation agents via mechanisms regardless of cholesterol levels. In HT patients, early induction of statin treatment is associated with a lower rate of acute rejection and GVD risk during the first year of follow-up, thus the administration of statins is recommended for all HT patients from week 1 or 2, regardless of cholesterol levels (recommendation degree I, evidence level A) [1].

   The risk of rhabdomyolysis is greater in transplanted patients due to concomitant CNI use which increases statin levels. Thus, it is essential to avoid the use of other drugs which increase statin levels like fibrates, azole antifungals, macrolides and calcium antagonists (diltiazem and verapamil). The risk of rhabdomyolysis is lower with pravastatin 20-40 mg or Fluvastatin 40-80 mg [1]. The withdrawal rate of statin treatment due to adverse effects or intolerance is low (under 5%) when there is close analytical monitoring and clinical follow-up [12].

2. Other common drugs for HT patients are those required to control comorbidities like HTN, osteoporosis, diabetes, etc. The chosen medications should be those that have the least pharmacological interaction with immunosuppressants.

2. REJECTION AND GRAFT VASCULAR DISEASE

» One of the most important reasons behind graft loss is driven by the patient's immune response to receiving a heart transplant. An immune pre-sensitized patient causes a hyperacute rejection; this reflects the immediate immune reaction of a patient against the graft and leads to immediate failure of the graft even before weaning from extra-corporal circulation.

» Acute rejection is often seen a few weeks after transplant and has to be treated intensively in order to preserve the graft and heart function. The most common type is chronic rejection, clinically seen in the appearance of coronary graft vasculopathy with diffuse hyperplasia of the inside of the coronary artery system.

2.1 Hyperacute rejection

Hyperacute rejection is now rare and occurs in the first minutes to hours post-graft implantation due to the presence of preformed circulating antibodies in the receiver directed against the graft vascular endothelium antigens. This causes inflammation, ischaemia and generalized myocardial necrosis usually with a rapid clinical progression.

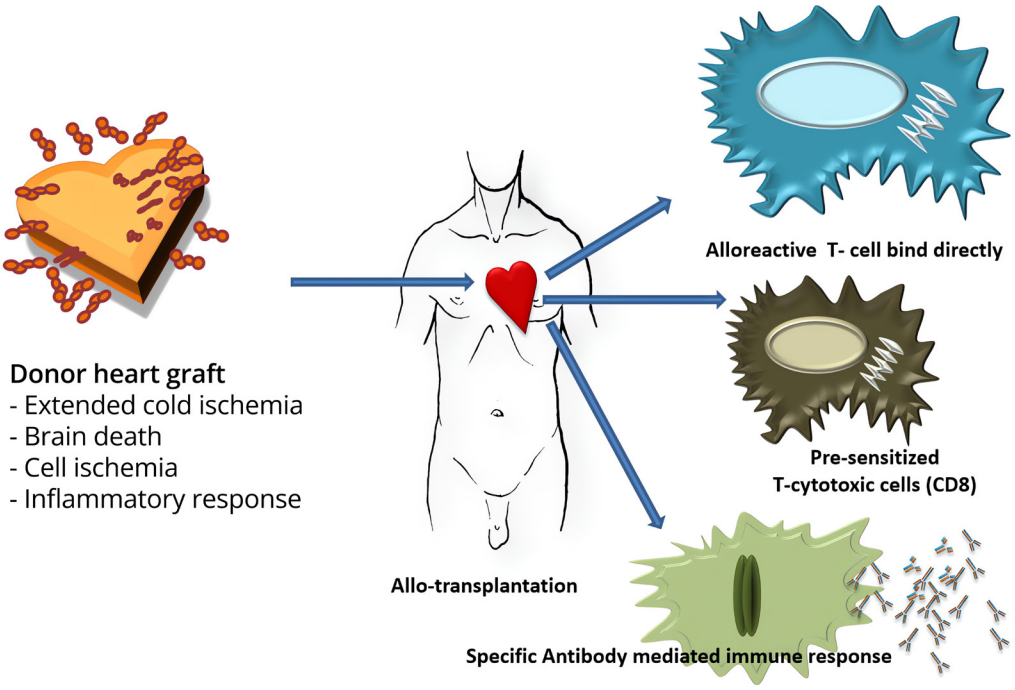

Figure 2.

2.2 Acute cellular rejection

Acute cellular rejection is much more frequent than hyperacute rejection, especially during the first 6 months post-HT. Approximately 20% to 40% of HT recipients will suffer at least one bout of acute cellular rejection during the first year. This is a T cell-mediated immunological response due to myocardial infiltration by inflammatory cells, oedema, and cell death, initially causing graft diastolic dysfunction and, if treatment does not commence in a timely fashion, it will cause systolic dysfunction and finally graft failure.

Table 3 shows two working nomenclatures recommended by the ISHLT for the histological classification of acute rejection from 1990 and the revised version of 2004 [13].

Table 3. ISHLT classification of acute cellular rejection

1990	2004
Grade 0 (absence of acute rejection)	Grade 0R
Grade 1A (mild acute rejection, focal) Grade 1B (mild acute rejection, diffuse) Grade 2 (moderate acute rejection, focal)	Grade 1R (slight interstitial infiltration and/or perimyocytic with single myocyte damage focus)
Grade 3A (moderate acute rejection, multifocal)	Grade 2R (2 or more inflammatory infiltrated foci with myocyte damage)
Grade 3B (borderline severe acute rejection) Grade 4 (severe acute rejection)	Grade 3R (diffuse inflammatory infiltrations with multiple myocyte damage foci, oedema, haemorrhage and vasculitis)

When should we clinically suspect the existence of an acute rejection episode?

Initially the symptoms are very non-specific (asthenia, dizziness, nausea, low grade fever). As ventricular filling pressures increase symptoms of left (effort dyspnea, orthopnoea and nocturnal paroxysmic dyspnea) and/or right (oedema, abdominal distension, etc.) congestion appear. Finally, with the deterioration of graft systolic function, low output symptoms may appear (somnolence, oliguria, hypotension and even frank cardiogenic shock). Likewise, myocardial inflammation may trigger auricular and ventricular tachyarrhythmia, bradyarrhythmia and AV block. The onset of such arrhythmias in a heart transplant patient should therefore always oblige us to rule out the onset of an acute rejection.

In the face of clinical suspicion of acute cellular rejection, and in order to avoid progression of myocardial damage, the following recommendations have been established [1]:

» Immediate commencement of treatment. Administration of endovenous steroid bolus constitutes the first line of treatment against symptomatic acute cellular rejection (recommendation degree I, evidence level C). In the event of haemodynamic deterioration, administration of cytolytic therapy with antilymphocyte antibodies should be considered (recommendation degree I, evidence level C). Table 4 details the standard guidelines used in treating acute rejection.

Table 4. Acute rejection treatment

	Medication	Dose	Duration
Cellular rejection without haemodynamic deterioration	IV methylprednisolone	**250-500 mg/day**	**3 days**
Cellular rejection with haemodynamic deterioration	IV methylprednisolone	**500-1,000 mg/day**	**3 days**
	+/-		
	IV thymoglobulin	**0.75-1.5 mg/kg/day**	**6-10 days**
Humoral or antibody mediated rejection	IV methylprednisolone +	**500-1,000 mg/day**	**3 days**
	plasmapheresis (+/- Ig IV)		
	+	**1 daily session or on alternate days**	
	IV rituximab		
		375 mg/m²/weekly	**4 weeks**

» Endomyocardial biopsy (EMB) should be urgently performed to confirm diagnosis (recommendation degree I, evidence level C).

However, with current immunosuppression guidelines, most rejection episodes are symptomatic. One of the challenges of HT follow-up is the early diagnosis of these episodes for their treatment, thereby avoiding any damage to the graft. In this respect, close clinical follow-up and routine control echocardiograms are useful tools. However, to date, periodical EMB are still the only guaranteed method to detect acute cellular rejection, particularly during year 1 post-HT, when the risk of rejection is greatest. Current recommendations for asymptomatic acute rejection vigilance are [1]:

» periodical EMB during first 6-12 months post-HT (recommendation degree IIa, evidence level C);

» after year 1, continued EMB control recommended for patients with high risk of rejection (recommendation degree IIa, evidence level C);

» treatment with steroid bolus recommended in asymptomatic rejection degree ISHLT ≥ 2R/3A (recommendation degree IIa, evidence level C).

2.3 Antibody-mediated rejection

A much less frequent acute rejection is antibody-mediated rejection (also called "humoral rejection"). This is a B cell-dependent rejection which produces antibodies directed against the graft vascular endothelium, and damage is essentially mediated by complement activation. It is associated with graft dysfunction, graft vasculopathy and a worse survival rate. This kind of rejection should be suspected when there is a graft dysfunction; however, an EBM shows no signs of cellular rejection unless it is low grade. Diagnosis and treatment are still controversial. The EBM diagnosis is based on histopathological (vascular involvement) and immunopathological (particularly, complement deposit in graft capillaries) findings. In accordance with the ISHLT consensus, here are four degrees of pathology antibody-mediated rejection (pAMR): pAMR0, pAMR1, pAMR2 and pAMR3, shown in Table 5 [14]. There is a general consensus on treatment when graft dysfunction exists. Treatment is aimed at eliminating, blocking or reducing antibody production and includes high dose steroid bolus, plasmapheresis, monoclonal antibody administration against B cells like rituximab (anti-CD20), thymoglobulin or intravenous immunoglobulins [15].

Table 5. Pathological classification of antibody-mediated rejection. ISHLT consensus 2011.

	EBM Findings
pAMR0 or Negative for AMR	H(-)I(-)
pAMR1 or suspected AMR	pAMR1-H:H(+)I(-); pAMR1-I: H(-)I(+)
pAMR2 or pathologically positive AMR	H(+)I(-)
pAMR3 or severely pathological AMR	H(+), I(+) and interstitial haemorrhage, oedema, capillary fragmentation, pyknosis, endothelial cells, etc.*

pAMR: pathology antibody mediated rejection; H: histopathology; I: immunopathology

*Usually associated with severe graft dysfunction.

2.4 Graft vascular disease

Graft vascular disease (GVD) is the main cause of morbidity and death during first year of HT. It is characterized by longitudinal diffuse concentric thickening of graft vascular tree intima affecting large epicardial arteries and coronary microvasculature. This vascular remodelling ends up conditioning serious impairment of blood flow to the graft myocardium with both diastolic (characteristic restrictive filling pattern) and systolic dysfunction. At five years post-HT 30% of patient will present some GVD factor. The aetiopathogenesis of GVD is not fully known, although current hypothesis is that it has a multifactor mechanism in which both immunological (chronic immunity response) and non-immunological (classical risk factors: atherosclerosis, acute rejection, CMV infection, etc.) factors intervene.

Clinical expression of this disease is unusual, whether as angina - due to denervation of the cardiac graft - or as myocardial infarction - due to the diffuse nature of the vasculopathy. As such, the disease usually progresses silently until its advanced stages, when signs and symptoms of HF appear due to graft dysfunction or sudden death occurs.

The most widely used method for evaluating GVD is conventional coronary angiography, despite its poor sensitivity given the diffuse nature of the disease. A coronary intravascular ultrasound (IVUS) is a more sensitive diagnostic method and the one of choice for intervention studies. A stress echocardiography may be useful in detecting GVD in patients unable to undergo invasive studies. The ISHLT recently established a GVD severity classification based on coronary angiography findings and graft function (Table 6) [16]. Early GVD diagnosis and prevention are essential pillars in HT follow-up given the asymptomatic nature of the disease until its terminal stage, so the following recommendations have been established [1]:

» Primary GVD prevention should include strict control of classical cardiovascular risk factors: smoking, HTN, dyslipidaemia, DM and obesity as preventive measures against CMV infection (recommendation degree I, evidence level C).

» Treatment with statins has been demonstrated to reduce the onset and progression of GVD, as well as long-term events, so it should be considered for all HT patients (recommendation degree I, evidence level A).

» An annual or biannual coronary angiography is recommended post-HT for early GVD diagnosis (recommendation degree I, evidence level C).

Table 6. Graft vascular disease classification according to ISHLT

ISHLT CAV0: Not significant	No angiographically detected lesion
ISHLT CAV1: Mild	LCT <50% or primary vessel >70% or any branch stenosis >70% (including diffuse narrowing) WITHOUT graft dysfunction
ISHLT CAV2: Moderate	LCT <50%, a single primary vessel ≥70% or branch ≥70% of 2 systems WITHOUT graft dysfunction
ISHLT CAV3: Severe	LCT <50% 2 or more primary vessels ≥70% or isolated branches ≥70% of 3 systems, or CAV1 or CAV2 WITH graft dysfunction (LVEF ≤45% or restrictive physiology)

CAV: cardiac allograft vasculopathy; LCT: left coronary trunk.

Once the disease is established, the therapeutic alternatives are limited and have poor efficacy. Use of mTOR inhibitors (proliferation signal inhibitors - PSI), sirolimus and everolimus, has been associated with a reduction in GVD at 12- and 24-months post-HT; however, their use is limited due to their adverse effects and a lack of information about long-term events. Although insufficient evidence is available, patients with GVD usually receive antiplatelet drugs based on the supposition that they have the same beneficial effects as for patients with arteriosclerosis. Percutaneous coronary intervention (PCI) may be contemplated in treating focal GVD lesions, although the restenosis rate is high, and the global impact on patient evolution is small. Surgical revascularization is reserved for very specific cases, like patients with high-risk lesions that are untreatable percutaneously. There is no evidence for the positive results of using vasodilators, betablockers or nitrates in patients with advanced GVD and HF symptoms. Diuretics are highly effective as symptomatic relief for these patients. In the case of refractory symptoms, the use of intravenous inotropes may be necessary. For terminal GVD patients, the only definitive treatment is a new HT.

Specific recommendations for treating established GVD are as follows [1]:

» Replacement of immunosuppression with mycophenolate mofetil (MMF) or azathioprine (AZA) for PSI should be considered (recommendation degree IIa, evidence level B).

» PCI with drug-eluting stents recommended for treating the appropriate focal lesions. Coronary revascularization surgery is an option for very specific patients whose lesions have bad prognosis and cannot be tackled with PCI (recommendation degree IIa, evidence level C).

» A new HT should be considered for terminal GVD patients without contraindications for a repeat HT (recommendation degree IIa, evidence level C).

» In conclusion, assistance for HT patients with acute HF symptoms with or without graft dysfunction requires hospital admission to relieve symptoms, confirm diagnosis and establish specific treatment. An EMB should be performed to rule out acute rejection in addition to a coronary angiography to confirm the diagnosis of GVD (Figure 3).

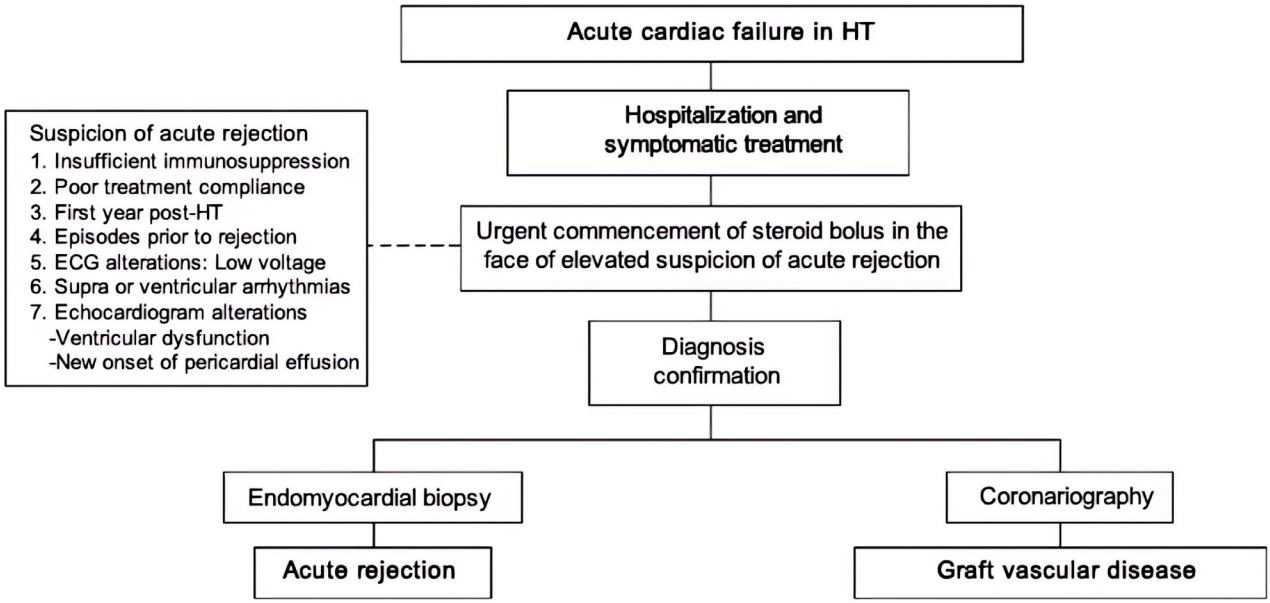

Figure 3. Acute cardiac failure in HT.

3. OTHER COMPLICATIONS

Other HT complications are mostly based on the direct or indirect impact of IS therapy on these patients. In particular, infections and neoplasms can be induced by chronic suppression of the immune system.

In addition, due to denervation of the transplanted heart, patients are more sensitive to arrhythmias and sudden death. A good medical follow-up is of great importance for these patients.

3.1 Infections

The need for immunosuppression post-HT means infection is still an important complication and one of the most common post-HT causes of death [5]. The frequency and aetiology of infection vary according to time elapsed since HT. Infections occur particularly within the first six months post-HT. Three types of infection may appear in the first month: asymptomatic - present in the recipient and exacerbated by the intervention; recipient - via an infected graft; and finally, those related to the surgery itself. Opportunist infections linked to immunosuppressive drugs are the most frequent between months 2 and 6. In particular, these include cytomegalovirus (CMV), *Pneumocystis jirovecii* (PJP), fungal infection (*Aspergillus*) and opportunist bacteria (*Listeria, Nocardia*). From month 6, with a reduction in immunosuppression, infections are more related to exposure in the community, in particular from community respiratory infections, food gastrointestinal infections, systemic mycosis and tuberculosis.

When treating HT patient infections, apart from their seriousness due to immunosuppression, one must also consider certain other aspects [17]:

- Specific early diagnosis is essential for the immunocompromised patient.
- Clinical and radiological manifestations may be scarce due to altered inflammatory response in these patients, which means more sensitive radiological techniques are required, such as a CT scan or MRI.
- Diagnosis should be preferably microbiological or histological. Serology has little value due to alterations in the humoral immunity of HT patients.
- On the aetiological spectrum, opportunist infections due to immunosuppression should be included.
- When choosing antibiotics, we must consider treatment urgency, overlapping toxicities and interactions with immunosuppressants.
- A reduction of immunosuppression may be useful during an acute process but includes the risk of graft rejection.

Table 7 includes prophylaxis for common HT infections including: *Pneumocystis jirovecii, Aspergillus, Mycobacterium tuberculosis, Toxoplasma* and CMV. The latter is particularly important since CMV is the most common infection among HT patients and involves deleterious effects not only due to the direct consequences of the infection, but also a variety of indirect effects including graft rejection, opportunist infections and GVD.

Table 7. Post-HT anti-infection prophylaxis

Agent	Recommendations	Treatment	Duration
P. Jirovecii	All HT patients	Oral clotrimazole 400/80 mg/d	6-12 months post-HT
M. Tuberculosis	Pre-HT tuberculin test* TBC history Close contact with TBC	Oral isoniazid 300 mg/d	6-12 months post-HT
CMV	1 All HT patients	IV ganciclovir 5 mg/kg/d* 14 days or oral valganciclovir 900 mg/d* + oral acyclovir 200 mg/8hr 3 months on completion ganciclovir/valganciclovir	4 weeks post-HT (with R-/D+ maintain 6 months)
	1 Anticipated therapy if: **a.** Ag CMV + or PCR CMV+ **b.** Acute rejection treatment with CS and prior CMV **c.** Acute rejection treatment with CS in HT (R-D+)	IV ganciclovir 5 mg/kg/12hr* or oral valganciclovir 900 mg/d*	7-14 days or until negative for Ag CMV or PCR CMV
Aspergillus	All hospitalized HT patients	Amphotericin B lipid complex inhaler 50 mg/week	Up to 3 months post-HT (daily first 4 days)
Toxoplasma	TC (R-D+)	Oral pyrimethamine 25 mg* Oral Lederfolin 15 mg/d	6 months post-HT
Oral Mycosis	All HT patients	Oral nystatin after meals	3-6 months post-HT
Oral Mycosis	All HT patients	Oral nystatin after meals	3-6 months post-HT

Ag: antigenemia; CMV: cytomegalovirus; CS: corticosteroids; D+: positive donor serology; R-: negative receiver serology; TBC: tuberculosis.

*Dose adjusted to kidney function

Note: Prophylaxis protocol may vary according to centres.

Regarding endocarditis prophylaxis, there is insufficient evidence to support specific recommendations for HT. However, the onset of valvulopathies in HT recipients is very frequent, and in the case of endocarditis, mortality is extremely high. Therefore, the use of antibiotic prophylaxis, particularly for dental procedures is considered reasonable.

3.2 Neoplasms

Neoplasms together with GVD are the main cause of late post-HT mortality. According to the Spanish post-HT tumour register date, the incidence of neoplasms after a 20-year follow-up was 14.4%. Among these, skin tumours constituted approximately 50% of neoplasms, followed by lymphoproliferative syndromes and to lesser extent solid organ tumours, particularly lung and prostate cancer [18,19].

Therapeutic treatment of a transplanted patient is not essentially different from that of the non-transplanted population. There is some evidence from experimental studies and kidney transplant that changes in immunosuppression guidelines with introduction of a PSI may delay the progression of post-HT neoplasms, so this practice is currently generalized [8]. In lymphoproliferative syndromes, a reduction in immunosuppression has been successfully used in combination with conventional cancer treatment [1].

As with the general population, the critical factor in handling post-HT neoplasms is prevention, and the established recommendations are:

- for HT patients, follow the recommendations established for the general population regarding screening for breast, colon and prostate cancer (recommendation degree I, evidence level C);
- close follow-up is recommended for skin tumours including annual dermatological evaluation (recommendation degree I, evidence level C);
- chronic immunosuppression should be minimized as far as possible in HT patients especially those with high risk of neoplasms (recommendation degree IIa, evidence level C).

3.3 Other complications secondary to chronic immunosuppression

Hypertension (HTN)

This is the most frequent post-HT complication and affects up to 95% of recipients at 5 years. It is directly related to the use of CNI immunosuppressants and corticosteroids (CS). To treat HTN in HT patients we recommend [1]:

- blood pressure targets and hygiene-dietetic measures are identical to the recommendations for the general population (recommendation degree I, evidence level C);
- drugs of choice for treatment of HT HTN are calcium antagonists, ACE inhibitors and AT1R blockers (recommendation degree I, evidence level C);
- correct adjustment of immunosuppression and CS minimization or suppression are useful strategies for controlling HTN (recommendation degree I, evidence level C).

Diabetes mellitus (DM)

Diabetes is a common complication in HT patients that affects 32% at 5 years. The use of CS is associated with a greater risk of DM post-HT, and CNI also have diabetic effects. Therefore CS-free immunosuppression systems and CNI dose minimization are potential strategies for the control and prevention of post-HT DM (recommendation degree I, evidence level C). However, these immunosuppression guidelines are not without controversy, due to an associated increased risk of rejection and an absence of demonstrated benefits in prolonging survival. For the treatment of DM in transplanted patients it is advisable to

follow the recommendations established by the American Diabetes Association (ADA; recommendation degree I, evidence level C) [1].

Chronic renal failure (CRF)

Deterioration of renal function is frequent post-HT and associated with a substantial increase in morbidity and mortality. Around 10% of patients present an estimated glomerular filtration rate (GFR) <30/ml/min/1.73m^2 at 5 years. Post-HT CRF is directly related to the use of CNI.

Bone disease

Only a minority of HT candidates have normal bone density. Among HF patients with functional class NYHA III or IV, the incidence of osteopenia and osteoporosis is 42% and 19% respectively. Post-HT bone density loss accelerates essentially in relation to steroid use, and to a lesser extent to the use of CNI. The incidence of vertebral fractures in HT patients is up to 35%, the majority of which occur in year 1. To prevent post-HT bone disease, we recommend that [1]:

- In the HT patient, regular weight load should be favoured and muscle strengthening exercises encouraged (recommendation degree I, evidence level C).
- In all HT adults, treatment with bisphosphonates should be initiated immediately post-HT and continue for at least the first year (recommendation degree I, evidence level B), maintaining long-term with calcium and vitamin D to prevent post-HT bone loss (recommendation degree I, evidence level C).

3.4 Arrhythmias and sudden death

When approaching the treatment of arrhythmia in the transplanted patient, it is essential to consider the denervation state of the cardiac graft, which is isolated from the receiver's autonomous nervous system. Most HT patients have a heart rate at rest of around 90 bpm, although some individuals may present sinus frequencies of up to 130 bpm without requiring any specific treatment [1].

Bradyarrhythmia are common post-HT operation, with an approximate occurrence rate of 20%. Treatment in the acute phase is with isoproterenol or heart stimulation and the evolution is generally favourable, with a current incidence of a definitive pacemaker implantation of 2%. Late bradyarrhythmia, i.e., beyond the 5th month are rare. In the case of symptomatic bradyarrhythmia requiring treatment it is worth remembering that atropine is inefficient due to graft denervation, so isoprenaline or heart stimulation should be used. Approximately half the symptomatic bradycardia or AV block cases are secondary to an acute rejection episode, treatment of which would resolve the problem. Should the existence of a reversible cause be ruled out, a definitive pacemaker should be considered.

The most frequent atrial tachyarrhythmia in HT is atrial flutter. On detection, an EMB is indicated to rule out acute rejection, since treatment could revert it. Should rejection be ruled out, given the high recurrence rate, the treatment of choice is radiofrequency ablation. The incidence of atrial flutter or fibrillation post-HT is 9-15% according to different series. Amiodarone is the drug of choice for treating atrial tachyarrhythmias in HT. Graft denervation makes it particularly sensitive to adenosine, since use of this drug at standard dosage may cause prolonged asystole, which must be borne in mind. Finally, beta blockers are generally not efficient in HT patients, although due to the possibility of partial graft denervation they may be useful for some patients.

Sustained ventricular arrhythmias are very rare in HT, obliging rejection or GVD to be ruled out. Sudden death may represent up to 10% of HT deaths, is usually GVD-related and occurs in the first year due to acute rejection. Controversy persists regarding the arrhythmic origin of sudden death in transplanted patients, as does the indication for an implantable cardioverter-defibrillator (ICD) as primary prevention for patients with advanced GVD. In this sense, descriptions exist of cases of sudden death in not ICD-rescued HT patients [20].

3.5 Non-cardiac surgery in HT patient

Evaluation of HT patients who are to undergo surgery must be conducted in collaboration with the transplant team responsible for patient follow-up. The recommendations for approaching non-cardiac surgery are [1,21]:

- Immunosuppression should never be suspended without prior consultation with transplant team responsible for the patient. Should oral administration of medication be impossible, continue with endovenous administration (recommendation degree I, evidence level C). Table 2 shows the dosage for conversion to intravenous of the main immunosuppressive drugs.
- PSI immunosuppression is associated with a delay in healing. Therefore, suspension of PSI treatment is recommended from approximately 5-7 days prior to surgery until 14 days afterwards. Treatment must be replaced with another immunosuppressant in accordance with patient characteristics.
- Regarding steroids, administration of an additional "stress" is recommended in HT patients who will undergo major surgery or those who receive a daily steroid dose >10 mg during the 3 months before surgery.
- Suspension of long-term treatment with bisphosphonates 3 months prior to any oral surgery is recommended due to the risk of mandibular osteonecrosis.
- Should blood product transfusion be necessary, preparations poor in leucocytes must be used (recommendation degree I, evidence level C).

CONCLUSIONS

- Long-term heart transplant (HT) survival has improved in recent years, essentially due to meticulous follow-up and improvements in immunosuppressive drug treatment.
- Consultation with the heart transplant team in the face of any dubious or emergency situation is compulsory.
- Induction immunosuppression therapy during the first days after HT is still controversial, although most teams support it.
- Maintenance immunosuppression is based on calcineurin inhibitors, antiproliferative drugs and steroids. Proliferation signal inhibitors are second line and a good alternative to the foregoing in certain indications.
- Acute cellular rejection is the main treatment target during the first years after transplant (particularly the first) and should always be suspected in the face of subtle symptoms.
- The only effective means of detection is a periodical endomyocardial biopsy, although work is being done to achieve non-invasive indicators for initial screening.
- Antibody-mediated rejection may cause severe graft dysfunction constituting a difficult diagnostic body.
- GVD is the main cause of morbidity and death after year one post-HT, besides being a silent process. Strict control of cardiovascular risk factors and use of statins are essential as alternative therapies are limited and have little efficacy.
- Immunosuppression-derived infection is a frequent problem in the first 6 weeks after HT, essentially due to opportunist agents of the recipient or transmitted by the donor. Diagnosis is difficult given the recipient's inflammatory response, so prophylaxis becomes necessary.
- Skin tumours and lymphoproliferative syndromes are the most common neoplastic processes during long-term follow-up. Use of proliferative signal inhibitors may play an important role.
- Other complications derived from immunosuppression therapy are HTN, diabetes, kidney failure, and loss of bone density.

Consultation with the heart transplant team in the face of any dubious or emergency situation is compulsory.

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TOPIC 6 - Unit 1

Indications and waiting list

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INTRODUCTION

The main objectives of a transplant are to improve survival and patient quality of life.

One of the principal problems that arises in candidate selection is choosing the optimum time or transplant window. The ideal transplant candidate has an advanced base disease with no other valid therapeutic option yet remains in a clinical condition that enables them to undergo the physical-psychological aggression of the procedure and survive time on the waiting list.

So, when deciding whether a patient is eligible for transplant we must evaluate:

- transplant survival;
- prognosis of the base disease;
- mean time on the waiting list.

1. INDICATIONS

Eligibility for patient inclusion on the lung transplant waiting list is based on the following criteria:

1. Advanced lung diseases with a poor survival expectancy (under 2-3 years):
   - » COPD and emphysema due to alfa-1-antitrypsin deficit.
   - » Bronchiectasis and cystic fibrosis (CF) (septic pathology).
   - » Interstitial lung disease (ILD).
   - » Idiopathic pulmonary fibrosis (IPF) or secondary to other interstitial pneumopathies.
   - » Primary or secondary pulmonary hypertension.
   - » Others: sarcoidosis, silicosis, lymphangioleiomyomatosis (LAM), pulmonary fibrosis associated with connective tissue diseases, etc.
2. Functional class III–IV.
3. Bad quality of life.

The indications for lung transplant have progressively increased, although the frequency of diseases varies by country. The results of the first registry created by Spanish groups were published in 2010 [3] and included data on 951 adults and 31 children. The most common lung transplant indication for adults in Spain is emphysema/COPD followed by idiopathic pulmonary fibrosis. These two diseases account for over 60% of all indications, with an increasing trend in the number of patients diagnosed with COPD (Table 1).

Table 1. Primary indications for adult lung transplantation. The Spanish Lung Transplant Registry (2006-2010)

	SLT	BLT	TOTAL
COPD	**135 (31.2%)**	**193 (37.3%)**	**328 (34.5%)**
IPF/UIP	**187 (43.2%)**	**74 (14.3%)**	**261 (27.5%)**
CF	**9 (2.1%)**	**108 (20.9%)**	**117 (12.3%)**
OTHER ILD	**33 (7.6%)**	**14 (2.7%)**	**47 (4.9%)**
BRONCHIECTASIS	**0 (0%)**	**39 (7.5%)**	**39 (4.1%)**
LAM	**11 (2.5%)**	**17(3.3%)**	**28 (2.9%)**
RETRANSPLANTATION	**18 (4.2%)**	**2 (0.4%)**	**20 (2.1%)**
IPAH	**1 (0.2%)**	**18 (3.5%)**	**19 (2.0%)**
OTHERS	**5 (1.2%)**	**14 (2.7%)**	**19 (2.0%)**
COPD WITH A1ATD	**8 (1.8%)**	**10 (1.9%)**	**18 (1.9%)**
SARCOIDOSIS	**8 (1.8%)**	**9 (1.7%)**	**17 (18%)**

A1ATD: Alpha-1 antitrypsin deficiency; CF: cystic fibrosis; COPD: chronic obstructive pulmonary disease; IPAH: idiopathic pulmonary artery hypertension; IPF: idiomatic pulmonary fibrosis; UIP: usual interstitial pneumonia; ILD: Interstitial lung disease; LAM: lymphangioleiomyomatosis.

However, data published by The International Society for Heart and Lung Transplantation (ISHLT) Registry in 2014, which included information on 47,647 lung transplants and 3,772 cardiopulmonary transplants in adults, show a progressive increase in the number of transplants for all indications [4]. Of these 47,647 patients, 45,697 underwent a primary lung transplantation and 1,950 were retransplants.

According to the ISHLT registry, the most common indications were COPD, non-deficit α1-antitrypsin (A1ATD) (38,2%), followed by ILD (24,3%), IPF (16%), and CF (16,4%) (Table 2).

Table 2. Primary indications for adult lung transplantation. ISHLT (1995-2013)

	SLT	BLT	TOTAL
COPD	**6,594 (43%)**	**7,078 (26.6%)**	**13,672 (38.2%)**
ILD	**5,354 (34.9%)**	**4,825 (8.2%)**	**10,179 (24.3%)**
CF	**234 (1.4%)**	**6,628 (24.9%)**	**6,862 (16.4%)**
IPF, other	**677 (4.4%)**	**970 (3.6%)**	**1,647 (3.9%)**
BRONCHIECTASIS	**62 (0.4%)**	**1,069 (4%)**	**1,131 (2.7%)**
LAM	**138 (0.9%)**	**302 (1.1%)**	**440 (1.1%)**
CONNECTIVE DISEASE	**177 (1.2%)**	**409 (1.5%)**	**586 (1.4%)**
IPAH	**92 (0.6%)**	**1,158 (4.4%)**	**1,250 (3.0%)**
OTHERS	**255 (1.7%)**	**515 (1.9%)**	**770 (1.8%)**
COPD WITH A1ATD	**771 (5%)**	**1572 (5.9%)**	**2,342 (5.6%)**
SARCOIDOSIS	**280 (1.8%)**	**776 (2.9%)**	**1,056 (2.5%)**

Despite being absolute numbers, an analysis of the different trends shows a drop in patients transplanted due to COPD, which has gone from 40% to 30%, whereas ILD-diagnosed patients have progressively increased from 17% in 1995 to 29% in recent years. A comparison of US and European centres shows that the former registry has a lower percentage of CF but higher ILD [4].

Part of the organs transplanted annually are used in patients with a previous history of lung transplant. The most common indication for retransplant is the onset of bronchiolitis obliterans syndrome (BOS) during follow-up. According to the international registry, the percentage of retransplants is higher in Europe and among young recipients [4]. This surgery may be performed on the already transplanted hemithorax, or on the non-intervened hemithorax for prior single lung transplant patients.

In routine clinical practice a patient with an active infection, a recent history of malignant tumoral disease (less than 5 years free of disease, except squamous skin tumours), toxic habits in the last 6 months, poor socio-familial support, a lack of treatment adherence or pathologies that irreversibly affect non-transplantable vital organs should not be considered eligible for lung transplant [5]. However, diseases like hepatitis B and C, HIV or some types of collagenosis, which alter immune response or have a supposedly short life expectancy are now considered unsuitable for lung transplant although they are not an absolute contraindication for it. In these situations, the clinical stage of the disease and each individual case are important.

Relative contraindications are resistant organism colonization, obesity (BMI over 30), over 65 years of age or other badly controlled medical conditions like DM, high blood pressure, hypercholesterolemia, etc.

Regarding the base disease:

COPD

Patients should be included on the list when they meet the following criteria:

- Patients with BODE index 7-10 or at least one of the following:
  - Hospitalization due to exacerbation with acute hypercapnia (PCO_2 >50 mmHg).
  - Pulmonary hypertension or cor pulmonale.
  - FEV_1 <20% and either DLCO <20% or homogenous distribution of emphysema in CT scan.

Patients should be referred to a transplant centre when their BODE index is over 5.

Cystic fibrosis and bronchiectasis

The main challenges a transplant poses for CF patients derive from chronic colonization of airways and the fact it is a systemic disease. Colonization by pan-resistant or multi-resistant germs prior to transplant increases the risk of posttransplant complications, although it is not a contraindication in itself. However, Burkholderia cepacia complex (BCC) colonization increases the risk of both premature and late mortality. Waiting-list patients are recommended to undergo a periodical (3-monthly) germ/bacterial culture and antibiogram, to ensure correct identification of pathogens and establish the most appropriate transplant prophylaxis treatment. Patients should be referred to a transplant centre if they meet any of the following criteria:

- FEV_1 <30%, or rapid FEV_1 deterioration, (particularly in patients under 18 NB: women have a poorer prognosis - consider earlier listing)
- Frequent exacerbations
- Recurrent or refractory pneumothorax
- Recurrent haemoptysis uncontrollable via embolization

Patients meeting any of the following criteria to be included on the waiting list:

- Respiratory failure
- Hypercapnia
- Pulmonary hypertension

Pulmonary fibrosis

A) Idiopathic interstitial pneumonias

Among the idiopathic interstitial pneumonias, the two most common are IPF with usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP). This group has a higher waiting-list mortality, so it is advisable to refer patients early.

Average UIP survival from diagnosis is 2.5-3 years, so these patients should be referred to a transplant centre immediately after diagnosis regardless of lung function. The evolution of an NSIP patient is more variable; however, those with a fibrotic pattern in the lung biopsy have an average survival rate of 2 years and should be referred early.

For IPF-UIP patients, transplant is indicated if they meet any of the following criteria with histologic or radiographical evidence:

» DLCO <39%

» A drop >10% in CVF during a 6-month follow-up period

» Desaturation below 88% during 6MWT

» CT scan with honeycomb pattern

For NSIP patients, transplant is indicated if they meet any of the following criteria:

» DLCO <39%

» A drop >10% in CVF or a 15% drop in DLCO during a 6-month follow-up period

B) Pulmonary fibrosis associated with collagen vascular diseases

Pulmonary fibrosis (with an NSIP or UIP histological pattern) is common in rheumatoid arthritis, scleroderma, etc.

There are no specific criteria for patients with collagenosis, however, in young patients with controlled disease, non-involvement of vital organs and without significant comorbidity, a transplant may be considered. Waiting list inclusion criteria are identical to IPF or NSIP.

C) Sarcoidosis

When evaluating patients with sarcoidosis for lung transplant, the following points are important: Thoroughly rule out the involvement of other organs (heart, liver, etc.) The presence of aspergilloma is not unusual, so this should always be investigated. The transplant indication established is for patients with NYHA functional class III-IV who meet any of the following criteria:

» Hypoxaemia at rest

» Pulmonary hypertension

» Right atrial pressure >15 mmHg

D) Lymphangioleiomyomatosis and histiocytosis X

The indication for transplant is established for patients with NYHA functional class III-IV who meet any of the following criteria: Hypoxaemia at rest, serious deterioration of lung function and/or exercise capacity.

Pulmonary hypertension (PHT)

The introduction of new PHT treatments has improved survival expectancy and reduced the need for transplant. Nevertheless, there is no drug which cures the disease, and a transplant continues to be an alternative for patients meeting at least one of the following criteria:

» Persistent NYHA functional class III-IV patients despite maximum medical treatment

» Poorly tolerated exercise at distance covered in the 6MWT under 350 metres

» Therapeutic failure with IV epoprostenol or equivalent

» Cardiac index <2 L/min/m^2, right atrial pressure >15 mmHg

Regarding transplant type, bipulmonary transplant is clearly established for septic diseases so as to pre-

vent contamination of the transplanted lung by the germs present in the native lung, as in the case of patients with bronchiectasis or cystic fibrosis.

Although single lung transplant is almost universally established for patients with a pulmonary fibrosis or interstitial pathology with negative cultures [6], for COPD there is greater debate due to the need to avoid problems the native lung may cause during follow-up. These include hyperinflation with a resulting compression of the transplanted lung, or superinfection due to previously unknown native lung colonization [7].

Occasionally, the type of transplant differs according to the experience of the service. So, the purpose of performing a single lung transplant is to increase opportunities for patients on the waiting list and reduce their mortality, with a 5-year survival in certain patients that is comparable to that of a bipulmonary transplant [8]. This is particularly the case for patients over 55 years, as it facilitates postoperative recovery due to less surgical trauma.

2. WAITING LIST

The main limiting factor for lung transplants is the shortage of donors. As already mentioned, according to the international registry, the number of transplants performed has doubled in compared to the previous decade [4].

The number of patients with terminal lung disease is much higher than the number of donors. This not only generates longer times on the waiting list, where patient quality of life worsens physically and psychologically, but also the possibility of patient demise while waiting. This highlights the importance of good lung donor management in addition to the generation of strategies to optimize prospective organs.

The Spanish National Transplant Organization (ONT) pioneered the development of a hospital coordinator network that facilitates organ detection, management, obtainment and distribution, and leads world statistics for organ donation by a wide margin.

Time on the waiting list results in worsening patient quality of life and an increase in mortality, with percentages that vary depend on the base disease. Death rates for CF reach 25%-30% and for PF this is 40-45% at 1 and 2 years after inclusion, respectively [9]. However, mortality on the US waiting list was 15.4% for each wait-list year between 2010 and 2012 [10].

Likewise, depending on recipient blood group and lung dimensions, waiting list times vary. Child recipients generally spend the longest time on the waiting list, making bench surgeries sometimes necessary to adapt donor lung size to the recipient's thorax.

The profile of brain death donors has also changed. Lung donors are older and have co-morbidities, which obliges a re-evaluation of selection criteria. Thus, a large percentage of donations are from patients who died from a brain haemorrhage, which in 2013 represented 66.2% of lung-donor deaths in Spain.

The ideal donor is under 55, a non-smoker or smoker who consumes less than 20 packets/year, has no history of thoracic trauma, with a normal chest X-Ray or CT, an absence of purulent secretions and a P/F ratio over 300. This is the donor profile currently present in 50% of cases.

Moreover, the lung is one of the most labile organs when preserving a multiorgan donor, so part of the success in obtaining donors depends on good management of the prospective lung donor in anaesthesia and ICUs for best preservation of valid lungs, including the rescue of some lungs initially deemed suboptimal [11].

Hypotension, hypothermia and the complications of insipid neurogenic diabetes with an onset *in situ*ations of brain death convert a multiorgan donor into a "critical patient," endangering the viability of organs for transplantation, and requiring maintenance of haemodynamic stability, good oxygenation and correct homeostasis.

Furthermore, the importance of the donor's detailed medical history should be emphasized, as should arterial blood gas (ABG) with an FiO_2 of 1 and PEEP of 5 cm H_2O, so donors can be classified as potentially usable (PaO_2 >300) or potentially recoverable (PaO_2 <300) lung donors, although a brain death patient should not initially be ruled out for lung donation. Note that radiological information should not be based on a single evaluation and a thoracic CT is advisable wherever possible.

Of 1,655 donors generated in Spain in 2013, 411 were offered as lung donors, with final lung extraction from 317 donors, of which number only the lungs from 237 (74.7%) donors were used [12].

Different groups have repeatedly endeavoured to solve these limitations; the use of non-heart-beating donors, which has already shown good results [13]; use of donors with extended criteria; single lung transplants or *ex vivo* systems used to recover lungs.

2.1 Suboptimal donors

All groups have found themselves in the situation of using donors with criteria that are considered suboptimal in some cases. One of the most questionable limitations is that donor age should be under 55. Various studies support the idea that as an isolated criterion, donor age should be flexible if the other parameters are within optimal values. Independently, this does not seem to be a variable that affects mortality, although it may be significantly associated with lower survival in combination with other factors, for example, prolonged ischaemia time [14].

There appears to be a relation between the incidence of primary graft dysfunction (PGD) and the use of donors aged 55, although it does not cause worse long-term survival. Moreno et al. report prevalence between 20% and 5.6% for primary failure (p=0.04) [15].

In their cohort of 94 patients transplanted between 1/2001 and 12/2002, of whom 24.5% received suboptimal lungs, Aigner et al. found no differences between days in ICU, intubation and hospital stay compared to the lungs of standard donors [16].

Nor do there appear to be differences in lung function posttransplant or in the incidence of re-admissions during follow-up [17]. Although during the first posttransplant years survival rates in both groups are similar, BOS and global mortality rates at 10 years are higher in recipients of lungs from donors over the age of 55.

A recently published paper summarizes the results of 10 studies comparing suboptimal donors with standard ones between 1993 and 2010, concluding that although long-term differences are similar, four found worse short-term results with a higher mortality at 30-90 days [18].

In conclusion, age alone is not a reason to rule out a prospective donor since, although the long-term survival rate may be lower than for optimal donors, use of this lung type offers an opportunity to patients who would otherwise die on the waiting list.

The frequency of donors over the age of 55 is increasing, and figures exceed 20%. Evaluating donor characteristics and recipient risk until a risk-benefit balance is reached represents the sole option for many lung transplant candidates.

However, the use of clearly suboptimal donors for clinically stable patients poses an ethical problem, since these donors may compromise a frequently complex post-operative period and lung retransplant in these conditions has a very high mortality rate.

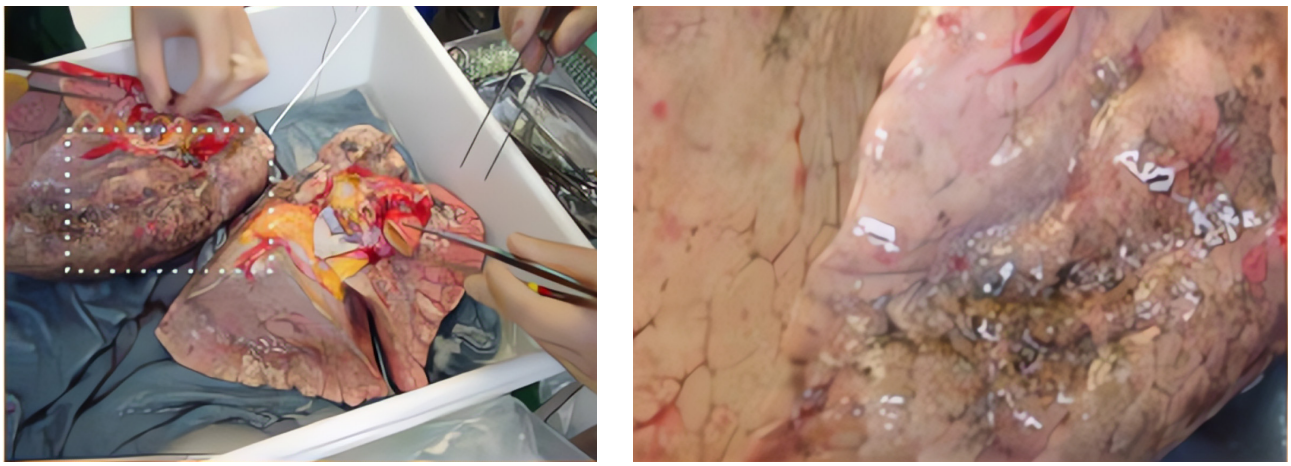

Figure 1. Long parenchyma; cancer, infection, subclinical emphysema, contusion.

2.2 Transplant type

One way of achieving maximum benefit from lung donors is single lung transplants. In recent years, the international registry has included approximately 50% single lung transplants compared to transplants as a whole [4], whereas this figure in Spain is 25-30 %. This strategy differs according to the experience of the different groups.

Single lung transplants enable two transplants from a single donor. The most efficient way to use donors is to perform both transplants in the same centre, known as "twinning." This was first conducted in Spain at Hospital la Fe in 1996 [19], and the La Coruña Team has published the largest experience [20].

2.3 Donors after cardiac/circulatory death

Use of donors in asystole seems an acceptable option provided there is an emergency medical service that enables rapid action and decision-making for in- and out-of-hospital cases.

The results of 29 lung transplants performed by the Hospital Puerta de Hierro group between 2002-09 [21] with uncontrolled asystole donors from Maastricht group II show a hospital mortality of 17%, a 1-year survival rate of 68% (compared to the global 79.3% in Spain) and 57% at 2 years. In these cases, CPR began within the first 15 minutes after the call. There was less than 120 minutes from the arrest to Perfadex® initiation and the subsequent cold ischaemia time, when the patient is subject to extracorporeal circulation, did not exceed 4 hours, which is the deadline for requesting family consent for organ donation.

In this series, PGD was G1, G2 and G3 in 5 (17%), 5 (17%) and 11 (38%) cases, respectively.

After analysis, the authors concluded that the highest PGD percentage could be attributed to high ischaemia time and lower survival, in comparison with results from series with standard donors. Therefore, we recommend stricter selection criteria than those currently used for other donors to reduce the incidence of PGD.

2.4 *Ex vivo* perfusion systems

Finally, another option currently available to increase donor pull is *ex vivo* lung perfusion (EVLP), which aims to recover conventionally extracted lungs that do not meet criteria as optimum, such as:

- » PO_2 below 300;
- » apparent oedema data or compatible imaging proof;
- » compliance problems during organ evaluation;
- » history of risk, e.g., transfusion of over 10 units of blood;
- » doubts about the existence of broncho-aspiration;
- » donor in cardiac arrest with over 10 min support.

Once standard extraction has been performed and the organ has been ruled out it would be sent to a transplant centre. The technique consists of placing cannulas in the atrial cuff and pulmonary artery, likewise an orotracheal tube for lung ventilation. This allows us to perfuse the lungs via a pump and add corticosteroids, antibiotics and heparin to the perfusion solution.

There are different types of *ex vivo* perfusion, with/without associated blood derivatives.

This system enables protective ventilation and recruitment of atelectatic areas. Likewise, fibrobronchoscopy can be performed to aspirate secretions and subsequently send samples for analysis.

During perfusion, serial controls are conducted of gases, and pressure measurements in the airway and pulmonary artery, in addition to control X-rays. A valid P02 to consider lungs for transplant is over 400 after the 6-hour observation deadline.

The pioneers of EVLP were the Stenn group at the University Hospital of Lund in 2001 [22], followed by the Toronto group [23], which is one of the centres with the largest number of donors recovered with this system.

The results presented in the last Toronto group paper [24] aim to analyse the long-term results of patients transplanted with EVLP donors, besides attempting to compare SPV, the incidence of chronic rejection, functional capacity and quality of life between these and recipients of lungs from conventional donors. Of the 403 transplants performed, 63 patients received an EVLP treated organ, and no statistically significant differences were found regarding survival, time free from chronic rejection, or in respiratory function tests like the highest predicted forced expiratory volume in 1 second. The authors therefore concluded this recovery system of suboptimal organs, most of which would otherwise be discarded, offers another option for patients who might otherwise die on the waiting list, with parameters in survival and quality of life comparable to those of conventional donors.

In 2012, the Vienna group presented their experience with 13 lungs subjected to EVLP and used for 9 bipulmonary transplants, obtaining similar results [25].

Different studies are currently aimed at ascertaining the results of recipients transplanted with lungs subjected to long-term EVLP systems, the viability of portable systems (portable Organ Care System (OCS) [26], and the use of EVLP to improve the conditions of lungs from donors after uncontrolled cardiac arrest [27].

CONCLUSIONS

- Based on organ availability and the outcome of the transplant, both recipient work-up and donor selection criteria are important. Although extended criteria donors should always be evaluated thoroughly, donor lungs are less impacted by comorbidity factors.
- Oedema and smoking habits have an impact on lugs, but donation after circulatory death seems to be successful in lung transplantation.
- Years of clinical experience and optimization of donor and recipient protocols have led to favourable outcomes. A thorough clinical work-up and strict patient selection is important.
- Although extended criteria donors should always be evaluated thoroughly, donor lungs are less impacted by comorbidity factors

[See bibliography for this unit at the end of topic 6]

TOPIC 6 - Unit 2

Organ evaluation and surgical procedure (techniques and surgical complications)

ORGAN TRANSPLANTATION

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INTRODUCTION

As already mentioned, the first step - and one of the most important stages - in the lung transplant process is organ selection and extraction from the prospective donor. Performing this procedure correctly determines the possibility, short- and long-term results of the transplant.

Longer survival for these patients has come thanks to ongoing developments and improvements in technical aspects, which are associated with better knowledge of possible intraoperative and postoperative complications.

1. ORGAN EVALUATION

The next two subsections explain the organ evaluation process:

» 1.1 Lung donor selection

» 1.2 Lung donor maintenance

1.1 Lung donor selection

The classical viewpoint of lung donation contemplates a brain death donor who meets the following criteria [28]:

» Under 55 years.

» ABG with FiO_2 100% and PEEP 5 cm H_2Og during 10 minutes with PO_2 >300 mmHg.

» ABO compatibility between donor-recipient.

» Chest X-ray with no abnormalities.

» No history of toxic habits. Non-smoker or smokes under 15 packets/year.

» Short time on mechanical ventilation (preferably under 72 hours).

» Absence of severe thoracic trauma.

» Absence of prior thoracic surgery or known pulmonary pathology.

» No signs of systemic or transmittable infection.

» No endobronchial aspiration data.

» No evidence of purulent endobronchial secretions and/or Gram-positive stain or positive culture.

» Negative serological studies for HIV, HCV, and HBV.

» Absence of neoplasms except low grade brain tumours, *in situ* uterine cervix carcinoma or squamous cell carcinoma.

» Visual and manual verification of the lung by the extraction team to check the state of parenchyma, thereby ruling out the existence of contusions-consolidations, tumours, etc.

Depending on the recipient's severity, or even on age, the transplant group may evaluate acceptance of donors with extended criteria:

» Over 55 years.

» Chest X-ray with small anomalies: small pneumothorax, pleural effusions, lung contusions or localized atelectasis. One of the lungs may be acceptable although the contralateral one lacks validity criteria.

» Prolonged mechanical ventilation (over 72 hours).

» Smoker of over 15 packets/year.

» Moderate fluid purulent endobronchial secretions, or prior positive culture for germs with good sensitivity to antibiotics (except *Candida*) and absence of accompanying pulmonary lesions, whether in chest X-ray and/or on lung palpation. In these cases, it is advisable for the extraction team to perform a fibrobronchoscopy on the donor before extraction to evaluate the amount and quality of secretions, obtain a bronchoaspiration sample for a Gram stain and wet mount examination for fungi, and to check the degree of bronchial inflammation.

The only unavoidable criterion is PaO_2 over 300, since this measures the lung perfusion and ventilation ratio and is the real indicator of good lung function. A lung no other contraindications than a P/F ratio below 300 is a good candidate for EVLP, enabling organ recovery and subsequent use.

The P/F ratio may be affected by different factors: A-a oxygen gradient, neurogenic lung oedema, fat embolism and pulmonary thromboembolism, of which the first two are potentially manageable and recoverable, either during organ extraction or with the subsequent application of EVLP. Finally, direct PO_2 measurement of pulmonary veins is correct and valid to check the donor's pulmonary gas exchange.

Once lung donor validity has been decided, it must meet certain compatibility criteria with the recipient. In recent years, a donor-recipient lung size matching study has become standard. The appropriate size essentially depends on height, gender and age; so special reference is made to these parameters for more precise chest cavity compatibility prediction, which is more reliable than chest circumference, vertical or transverse diameters. Height, gender and age have been related using a mathematical formula which calculates the so-called donor-recipient predicted total lung capacity (pTLC).

Note that in a single lung transplant, it is preferable to have a larger organ than the ones extracted (particularly if the recipient is emphysematous, although also for patients with fibrosis or pulmonary vascular disease). In recipients of a bipulmonary transplant with COPD, a larger implant size is equally admitted. For patients with fibrosis or pulmonary vascular disease, organs of a similar size or slightly smaller than the original thoracic volume (some authors propose up to 20% less) are preferable since the surgical procedure is more straightforward and chest closure has less risk of tamponade.

However, many groups currently prefer lungs with a pTLC ratio (pTLC donor/ pTLC recipient) greater than one. Various authors have demonstrated better survival particularly in a bipulmonary transplant [29,30]. Conversely, other groups conclude that large differences in size both above and below the predicted value may be considered valid without affecting long-term survival, thereby increasing the possibilities of obtaining an organ for waiting list patients [31].

In certain cases where there are large anthropometric differences between the donor and recipient, there are clear associated technical difficulties, both during implantation and on chest closure. This means that reduction surgery is necessary (a typical resection or lobectomy), which is generally performed during bench surgery and also reduces serious atelectasis incidents secondary to size difference during the postoperative period.

1.2 Lung donor maintenance

Maintaining the multiorgan donor is essential, as is providing specific care for each organ to be transplanted, generally keeping them in good condition until their extraction from the donor. Particular attention should be paid to perfusion, due to the specific physiopathology associated with brain death, regardless of the cause of death.

When spontaneous respiration ceases there is a loss of circulatory control, bringing an onset of haemodynamic alterations, thermal dysregulations and different endocrine-metabolic alterations which are part of this specific physiopathology.

Lung donors require special attention to maintain correct gas exchange and therefore optimal organ functionality. The onset of pulmonary oedema and bacterial colonization, largely secondary to the artificial ventilation required are the main problems which cause premature deterioration of donor lungs. Special monitoring and assistance are therefore required to provide the recipient with the best organ possible, one which most closely resembles the definition of an "ideal lung donor." This not only enables correct organ maintenance but also, with correct management, the recovery of prospective donors, which may increase the number of transplants at a centre [32,33].

Generally, these measures include:

» recruitment manoeuvres related to the protective ventilation associated with visible improvements in PaO_2/FiO_2 and chest X-ray;

» fluid restriction and administration of diuretics;

» techniques to prevent bronchoaspiration, such as raising the donor's headboard 30º or maintaining endotracheal balloon pressure at 25 cm H_2O [34].

Multiorgan donors in general, and lung donors in particular, must always be considered "critical condition patients" and pursuant to this, establish broad-ranging monitoring, good ventilation support management, correct treatment of lung oedema of neurogenic origin, and avoid both general and lung infections [35,36].

Monitoring

Continuous electrocardiogram with 2 leads, preferably V5 and aVF or D-II, to keep heart rate under 100 bpm, with special attention to the possible onset of arrhythmias (most frequent are extra-systole and conduction disorders) and/or major changes in electrocardiographic morphology particularly ischaemic alterations.

» Invasive continuous monitoring of arterial pressure via intra-arterial catheter, preferably inserted in the radial artery, attempting to maintain systolic pressure equal to or over 100 mmHg.

» Lung function will be monitored using continuous pulse oximetry, capnography and a series of ABG as often as necessary. The aim is to achieve an SaO_2 over 95%, maintaining normocarbia via correct respirator adjustment; pH must be within the normal range of 7.35-7.45.

» Hourly monitoring of diuresis, which must exceed 1 ml/kg/hour but bear in mind the frequent onset of polyuria in brain dead patients due to insipid diabetes which must be correctly treated.

» Continuous temperature monitoring via insertion of a retropharyngeal thermometer. Donor must be kept in normothermia; heating perfusions should be administered whenever necessary, with insertion of a heater in the inspiration branch of the respirator, lavage of nasogastric tube with hot saline serum, use of a thermal blanket, etc. as required.

Ventilation support

A critical point in donor maintenance is obtaining correct tissue oxygenation to keep transplantable organs in good condition. Maintenance of cardiac output, haematocrit within acceptable limits, and correct ventilation are basic parameters on which oxygen transport depends, therefore maintain normoxia.

However, we should bear in mind the high frequency of alterations in gas exchange which may occur in the artificially ventilated prospective donor. These include pulmonary oedema, atelectasis, haemothorax or pneumothorax. While these alterations are important in the multiorgan donor, they are an unavoidable priority in the prevention and treatment in a lung donor.

Therefore, particular care must be taken with ventilation, using a volumetric respirator and bearing in mind the following guidelines:

» Use of minimal FiO_2 necessary to maintain SaO_2 over 95% (or PaO_2 over 100 mmHg), without surpassing FiO_2 of 0.4, to avoid possible oxygen toxicity of lung tissue and formation of absorption atelectasis.

» PEEP of 5 cm H_2O should be applied to maintain lung volume, recruiting the maximum number of alveoli, thereby avoiding collapse with the formation of atelectasis.

» It is advisable to avoid high peak-inspiration pressures (should not exceed 25-30 cm H_2O), recommendations are the use of current volumes between 10 and 15 ml/kg, combined with adjusted respiratory frequency in accordance with the $PaCO_2$ values obtained in ABG.

» Intubation performed via low pressure silicone tube. Keep the tracheobronchial tree free of secretions; however, aspiration should only be performed when strictly necessary using utmost asepsis.

Neurogenic pulmonary oedema

After brain death there is usually a tendency to an onset of progressive deterioration of lung function generally related to phenomena of microembolization, fat embolism or secondary to a massive supply of liquids during initial resuscitation. However, on other occasions, abnormalities observed in lung function may be a direct consequence of brain damage.

During the initial stage of brain death there is a massive catecholamine release that can cause the loss of alveolo-capillary membrane integrity in the lung, permitting passage towards the albumin alveolus and other macromolecules. Thus, pulmonary oedema with an onset of neurogenic origin is characterised by a protein-rich liquid transudate towards the alveolar space.

There is no specific neurogenic treatment, although correct treatment includes maintenance of PEEP 5 cm of H_2O already mentioned as advisable for any prospective lung donor and a correct intravascular volume expansion, using the same parameters as for CVP and PCP control as a basic guide. Use of inotropic agents may also be necessary.

Note that one of the determining, and perhaps most important, factors for the onset of neurogenic pulmonary oedema is the time elapsed between the diagnosis of brain death and organ extraction, taking into account that the longer the delay, the higher the probabilities of the onset of this condition.

Lung infections

A problem which often impedes lung donation is the high incidence of infections present in this organ among multiorgan donors.

Donors are necessarily subject to intubation and mechanical ventilation, which leads to a rapid colonization of airways and frequent subsequent infection of pulmonary parenchyma. Moreover, the majority may have been aspirated either with the onset of the pathology which subsequently led to brain death or during initiation of resuscitation manoeuvres.

There may also be some kind of associated trauma in patients who have vesical, nasogastric, venous or arterial catheters, which favour the entry of micro-organisms and the onset of infection.

Infectious complications are a major cause of death in lung transplant patients, among whom bacterial pneumonia is the most common. For this reason, antibiotic prophylaxis is recommended in the donor, either a third-generation cephalosporin or specific antibiotic in accordance with the results of sputum cultures obtained from tracheobronchial fibrobronchoscopy aspiration.

The most frequently found pathogens in studies on donors are *Staphylococcus, Enterobacteria, Acinetobacter* and *Candida*, and the studies highlight that in 97% of cases at least one micro-organism developed in the culture.

2. SURGICAL PROCEDURE. COMPLICATIONS

The next subsection deals with:

- Lung extraction
- Bench surgery
- Lung transplant
- ECMO
- Surgical complications

2.1 Lung extraction

From a technical perspective, lung extraction is mainly performed on a multiorgan donor. Note that this surgery varies compared to other thoracic surgeries, since many of these procedures are performed outside the conventional OR where the extraction team is used to working.

Good co-ordination between the different extraction teams during the intervention will enable the largest number of viable thoracic and abdominal organs.

Another consideration is the need for good communication with the transplant team so that times can be adjusted as far as possible, thereby reducing organ ischaemia time.

Technical aspects

The technical aspects of extraction today are standardized, and the result of small variations made to the classic technique described by Cooper and Pearson [28,37]. Broadly speaking, and with possible changes in some groups, the procedure is as follows.

Firstly, on arrival at the hospital, the extraction team must confirm the information conveyed to the surgeon, paying particular attention to the importance of checking blood group, measurements of both lungs, pathological history, cause of death and respiration-haemodynamic stability.

Optimization of the donor situation may be necessary in the OR, attempting to emphasize a negative balance of liquids and evaluate the need for diuretics, use of corticosteroids and recruitment manoeuvres. Occasionally a fibrobronchoscopy is necessary before diagnosis-treatment, with the possibility of ruling out prior bronchoaspiration, aspirate secretions, transudate, foreign bodies, etc.

One or more repeated ABG with FiO_2 100% and PEEP of 5, that confirm pO_2 is maintains values >300-350.

A central level sample from both aorta and pulmonary veins may occasionally be useful, either to confirm oxygenation of lungs individually, ruling out a possible peripheral shunt due to unilateral pulmonary alterations, or to confirm their correspondence with peripheral blood values. This requires the haemodynamic stability of the donor, and occasionally requires modification of the operating table to the Trendelenburg position to improve preload and avoid hypotension associated with cardiac manipulation. Sampling of right pulmonary veins is performed after retracting the right atrium. For left pulmonary veins the manoeuvre is similar but on the left ventricle. In special situations, the pulmonary artery of one lung considered invalid may be clamped to perform a selective ABG and confirm the validity of the other.

Middle sternotomy

Extraction commences with a standard middle sternotomy, usually extended to pubis for abdominal organ extraction. The anaesthetist is required to perform an apnoea manoeuvre on opening the bone with a mechanical saw to prevent possible injury to pulmonary parenchyma.

Lung inspection

On opening both pleurae, the lungs are manually and visually evaluated to rule out the existence of atelectatic areas, tumoration, consolidations, contusions, bullae, adherences, etc., depending on the patient's history. Next, attempts are made to improve reversible findings, generally atelectasis, with recruitment manoeuvres and confirmation of their resolution.

After checking all of the donor's details, direct evaluation of lungs and maintenance or improvement of gas exchange at time of extraction, the team responsible for implantation is given confirmation of validity and the report.

Opening the pericardium and dissection of large vessels

Next, the pericardium is opened in an inverted T, and pericardial traction silks are placed to improve the surgical field in order to proceed with the dissection of vessels. The ascending aorta is dissected to prepare clamping and prevent a possible lesion of the right pulmonary artery crossing its lower face. Next, a tourniquet of the surgeon's choice is applied. If there is a heart extraction, dissect the upper and lower venae cavae. Next, dissect the pulmonary artery trunk, separating it from the aorta. In heart extraction, the cardioplegia cannula is then inserted in the ascending aorta.

Pulmonary artery cannulation

After this step, make a tobacco-pouch suture with 4-0 Prolene on its anterior face, halfway between the pulmonary valve and the division. If the other teams are ready to cannulate, there is prior infusion of the heparin dose calculated in accordance with donor weight (3 mg/kg), insert the cannula in the tobacco pouch. A child aortic cannula nº 12 -16 is used in accordance with artery size.

Prostaglandin E perfusion

Start prostaglandin perfusion. Administer an ampoule of 500 mcg PGE1 diluted in a 50 cc drip of glucose serum at 5%. Ensure perfusion is slow because it can cause brusque hypotension in patient.

Pulmonary preservation liquid perfusion (Anterograde pulmonary preservation).

The preservation solution used is intracellular with a low potassium content.

Clamp the thoracic aorta, ligate upper vena cava, and start anterograde perfusion (60 ml/kg donor weight) at 4-8º, with system decompression via incision of lower vena cava and left atrial appendage. Solution bags will be placed at sufficient height to maintain a perfusion pressure 15-20 mmHg (+ between 50-60 cm above chest). Next, proceed to 15 ml/kg via retrograde path, prior to lung extraction or bench surgery prior to implant, administered at a pressure of 10-15 mmHg.

When transplants began, modified Eurocollins solution was commonly used; however, experimental and clinical evidence suggested better lung preservation solutions with low potassium content (LPD solution). Its clinical use has shown fewer heart rhythm alterations due to hyperpotassaemia, and fewer reperfusion problems, so LPD solution has been adopted as standard preservation by most groups. Both Perfadex® and Celsior Solutions®, which are also low in potassium seem, to achieve good results [38].

At this point in the extraction, cold ischaemia time starts, during which it is important to maintain the lung surface at the lowest possible temperature, so continuous cold serum instillation is added to the low temperature Perfadex solution to both hemithorax (at 4ºC).

Until then, the lungs are kept ventilated with FiO_2 0.4 or sufficient to maintain saturation between 95-100% and PEEP 3-5 cmH_2O.

Cardiectomy

The left atrium (LA) is opened approximately 3 mms left of the pulmonary vein entry on the anterior face. Entry of right pulmonary veins seen from inside the LA, continuing the interatrial groove section, leaving a 5 mm cuff. This is the most delicate part of lung extraction, when there is heart extraction, since a small round piece of atrium muscle tissue of at least 3-5 mm must be left that includes the 4 pulmonary veins with sufficient atrial wall margin for suture with the recipient's atrium. The LA section is finished leaving the posterior face field. The cardiectomy is completed sectioning the ascending aorta, pulmonary artery at bifurcation level, and the venae cavae.

Lung extraction

After heart separation and extraction, lungs are separated from the posterior mediastinum starting via the pericardial section at lateral and posterior level of the lower pulmonary ligaments. Existing pleuro-pulmonary adherences are liberated. The left lung is brought to the right cavity, longitudinally dividing the mediastinal pleura upwards above the oesophagus. The descending aorta is sectioned. Both lungs are brought towards the left pleural cavity and the remaining mediastinal pleura is divided along the oesophagus anterior face until reaching the distal trachea. Finally, the lungs are inflated again and proceed to trachea section between double mechanical suture (TA-30 with green load), maintaining average inflation of both lungs.

Storage and transport

On completion of the procedure, away from the field, check the correct state of all structures. Introduce the bipulmonary block in the first sterile plastic bag surrounded by leftover perfusion preservation fluid, and hermetically close with its tape. Next, introduce it into a second bag containing very cold serum but not ice, which is harmful for the pulmonary parenchyma, so it covers the lungs. Close and place in the third and final security bag, which must also be correctly closed.

Bipulmonary block extraction is always performed, even if one of the lungs is invalid or will not be implanted for other reasons, in which case it will be sent for histological analysis to detect anomalies.

Occasionally, each lung is shared by two recipients in different hospitals. In this case, both grafts are separated, sectioning the main left bronchus between two mechanical sutures with TA-30 green, at main carina level. Each lung is prepared separately for transport as previously described.

Given the limited tolerable ischaemia time of lung grafts -most authors refer under 6 hours as the ideal and a maximum of 8 hours [39] - it is essential to adjust the times between extraction and implant as closely as possible, so that when the lung graft reaches the hospital it can be implanted in the recipient immediately and revascularized.

Co-ordination between the extraction and implantation teams is essential to achieve this.

The distance between the donor and transplant hospitals is an important factor to consider when organizing the procedure, as are the recipient characteristics (initial predicted outcome of complex surgery due to adherence or previously known interventions), or number of organs to extract, since this may cause delay or bring forward the start of a procedure. Usually, the aim is to initiate explant from the recipient on confirmation of validity with the following sequence: Anaesthesia begins on confirmation of lung validity and after aorta clamping. Surgery starts on completion of lung extraction, checking the organs are correct. No irreversible steps are taken on recipient until arrival of the lungs and their final preparation for implantation begins.

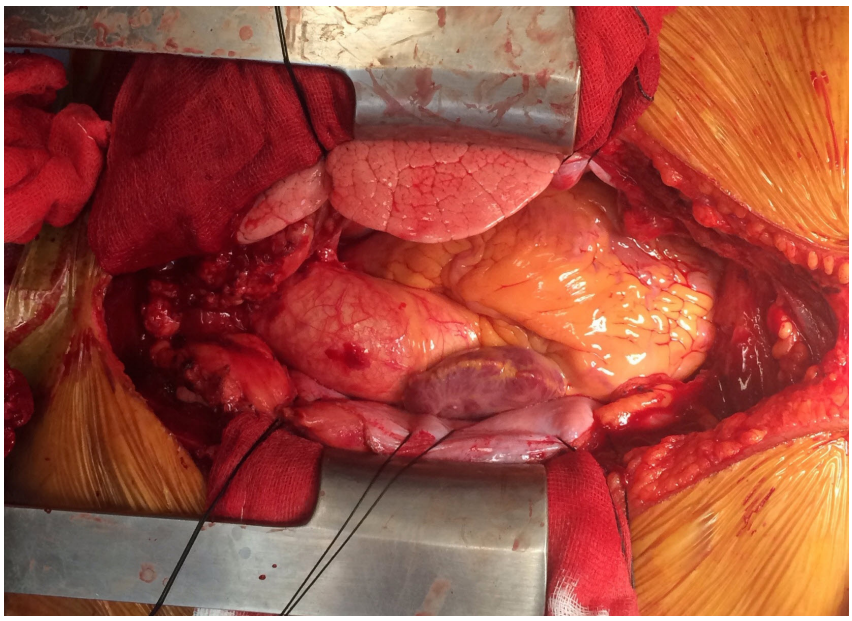

Figure 1. Extraction surgery. Middle sternotomy.

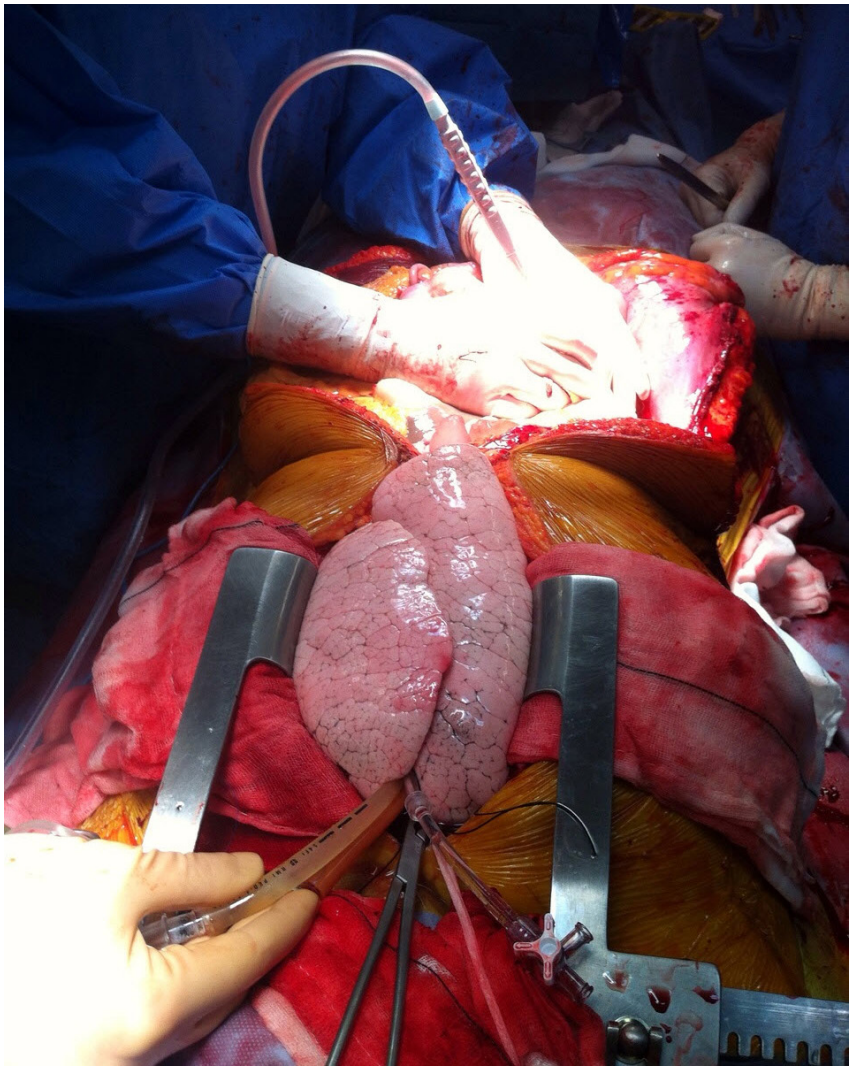

Figure 2. Pulmonary preservation liquid perfusion.

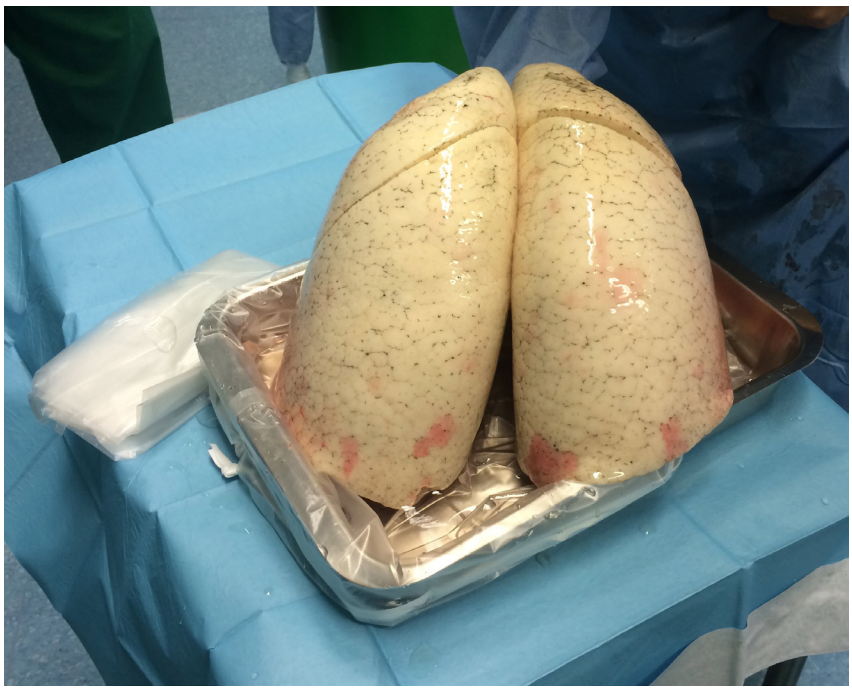

Figure 3. Storage and transport.

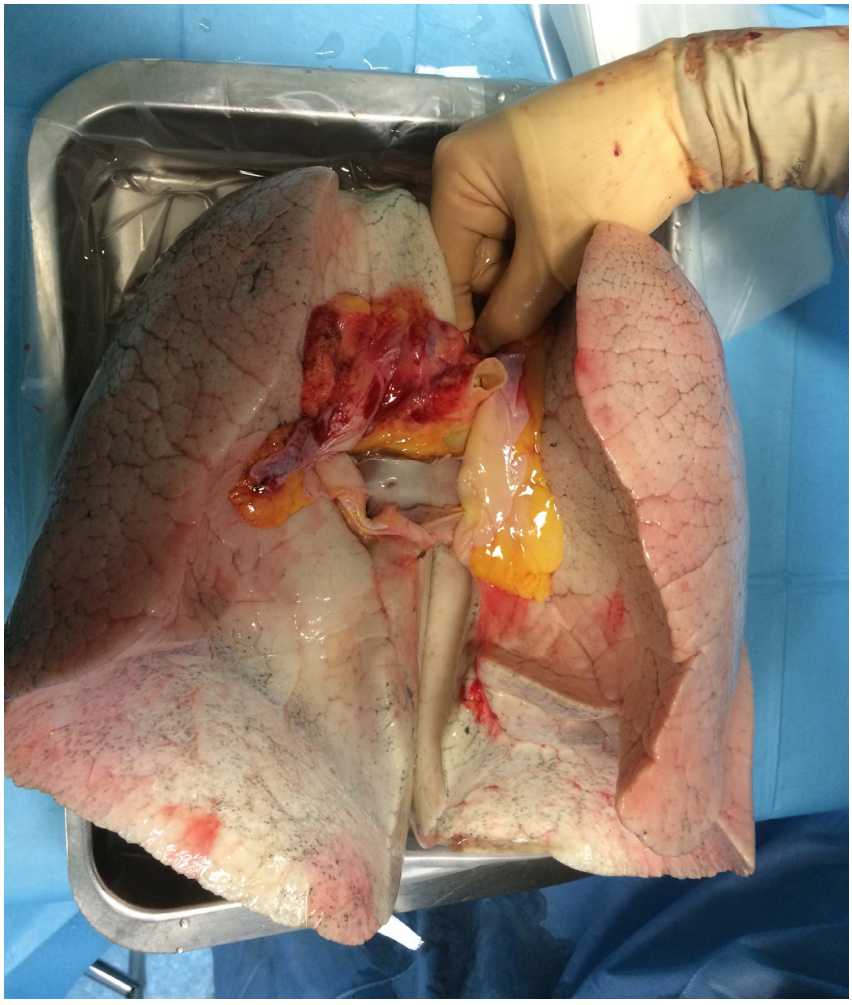

Figure 4. Checking the correct state of all structures.

2.2 Bench surgery

Final preparation of the lung grafts begins on their arrival at the transplant hospital. Usually, the surgical implant team is ready to perform the pneumonectomy.

The bag is removed from the transport cooler and the outer bag is removed. The bench surgeon takes the pulmonary block and takes a sample of the liquid surrounding the lungs (sterile tube of 10 ml), removing them from the third bag and introducing them into a large container with cold serum.

The good condition of the lungs is checked again, and recipient lung explant begins.

The posterior face of left atrium is sectioned in the medial area. Vascular structures of both pulmonary hila are cut (pulmonary atrium and artery) leaving them prepared for surgery (Figure 5).

Remove the excess of pericardial or mediastinal pleura but leave a flap rich in fat over the bronchus to perform surgery over the bronchial suture.

The lung to be implanted first is separated, suturing the main bronchus level with the main carina using TA-30 green and immediately sectioning it below. The other lung is stored, maintaining its inflation, in two bags and a cooler with ice.

A sample is taken of lung bronchial secretions with a swab, and the bronchial tree is cleaned with an aspirator, instilling physiological serum if necessary. The bronchus is cut back 2-3 rings from its division.

Next, retrograde pulmonary perfusion is performed, if it was not done during extraction, inserting a cannula into the pulmonary veins and perfusing the same solution used during extraction for retrograde perfusion 15 ml/kg 10-15 mmHg pressure with the liquid leaving the pulmonary artery totally transparent. This perfusion enables lavage of the lung vascular bed for haematic remains, air bubbles and fat, besides being described as completing preservation of bronchial circulation and improving lung graft function [40]. During this perfusion, the lung should be ventilated by introducing an intubation tube in the bronchus connected to a ventilation system with a filter and an Ambu bag.

Check and repair any anomaly existing in the lung whether a vascular tear or a bulla resection.

Should a mismatch occur due to larger donor size, lung resection will be necessary.

To alleviate the shortage of donors and in consideration of their idiosyncrasies, some countries perform a lobe or bi-lobe transplant from a living donor. This technique appeared in the 1990s and was aimed essentially at patients in very bad clinical situation who would not survive a prolonged time on the waiting list. Generally, these recipients are patients in a worse condition than deceased donor recipients [41]. The principal aim of the extraction is to ensure the donor's well-being. Generally, co-ordination between extraction and implantation teams is straightforward, since it is performed in the same centre, and the donor characteristics mean the graft is not affected by typical hormonal and haemodynamic changes of a brain death donor, thus obtaining results that are comparable to conventional transplants in this subgroup.

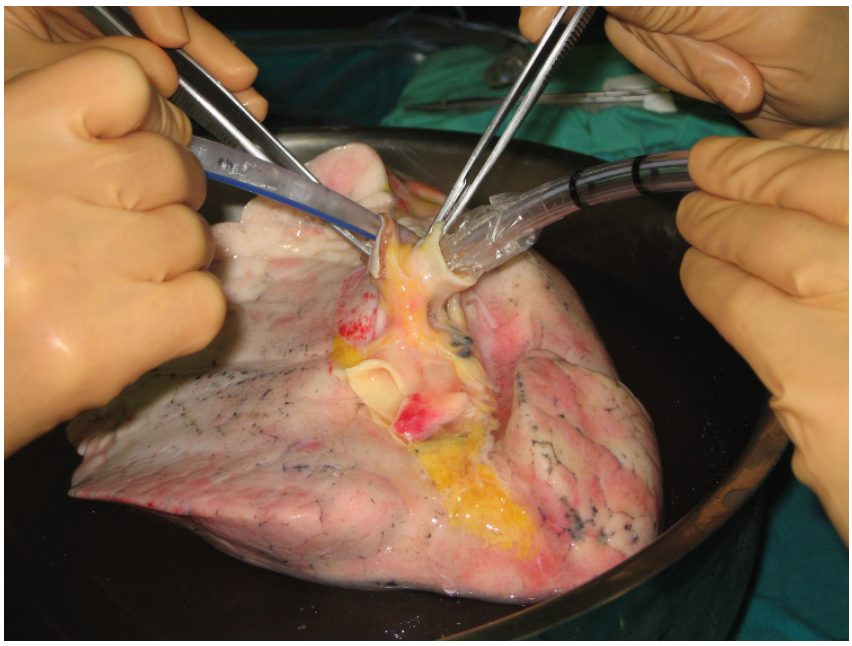

Figure 5. Bench surgery.

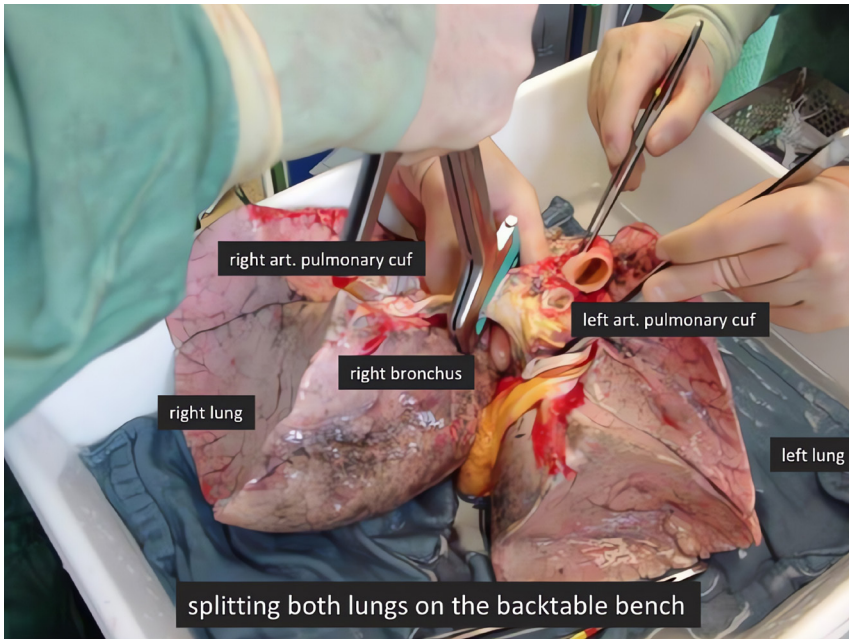

Figure 6. Splitting both lungs on the back table bench.

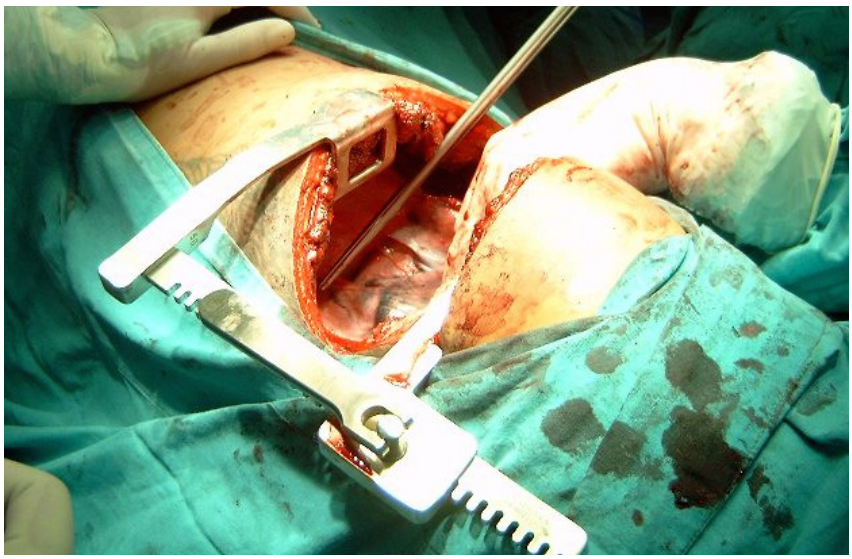

Figure 7. Surgical approach. Thoracotomy. Single lung transplant.

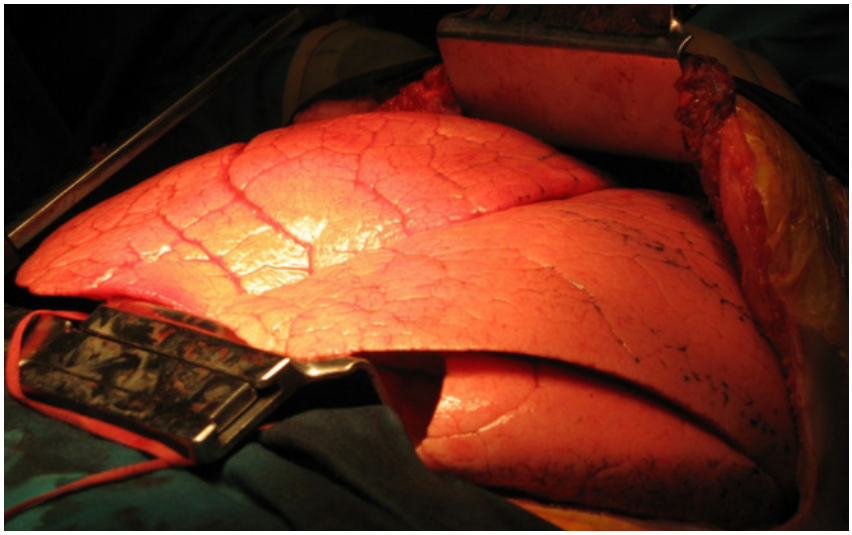

Figure 8. Surgical approach. Clamshell. Bilateral lung transplant.

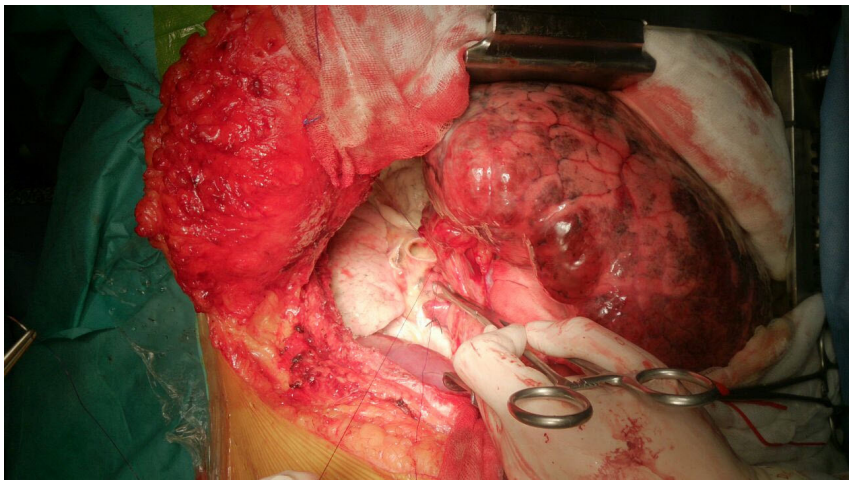

Figure 9. Bronchial suture. Membranous portion with continuous suture.

2.3 Lung transplant

The works of Veith [42], Pearson, Cooper or Patterson [43,44] in the 1980s established the technical bases that facilitated that start of clinical transplants. The techniques have been slightly modified and refined since then based on acquired experience.

2.3.1 Single lung transplant

Indicated in non-septic pathologies, such as patients with restrictive-interstitial pathology or emphysema not colonized in previous cultures by multi-resistant germs.

The aim is to increase the number of transplants, optimizing the use of organs, e.g., in 2012 according to Spanish National Transplant Organization data, confirmed patients on the lung transplant waiting list in 2012 for single lung presented a 53% probability of being transplanted compared to 44% of those awaiting bipulmonary transplant.

Likewise, single lung transplant usually represents a more straightforward surgery due to the lower global ischaemia time, less use of EEC, occasionally allowing early orotracheal tube removal, less postoperative pain, and a lower incidence of diaphragmatic paralysis. Therefore, it presents a great advantage for patients over 55-60 who are on waiting lists [45,20] and have associated comorbidities and risk factors.

The indication for single lung transplant widely admitted by most groups is idiopathic pulmonary fibrosis (IPF) and lung diseases with predominant restrictive spirometry (lymphangioleiomyomatosis, histiocytosis, etc.).

It is important to bear in mind that waiting list patients with pulmonary fibrosis represent the second most common pathology of patients who "code" due to clinical worsening. Therefore, listing these patients as prospective recipients of a single lung transplant increases their possibility of receiving an organ [46,47].

For emphysema, a single lung transplant presents the inconvenience of mediastinal displacement towards the transplanted lung due to possible hyperinflation of the native lung and subsequent contralateral compression. The habitual symptoms are a reduction of functional capacity and exercise tolerance once other causes have been ruled out. This can be controlled by choosing donors with a lung size 1.2-1.5 times bigger than corresponds and preferably performing a right-side transplant, enabling the native lung to displace the left diaphragm in the event of hyperdistention, a reduction in volume in the transplant surgery, or in the long-term, depending on patient evolution [8].

The transplant is usually performed of the side with least perfusion in order to preserve the best organ and improve patient tolerance of pneumonectomy prior to implantation. In the event of similar perfusion and a history of previous thoracic surgery or trauma in one of the hemithorax, the transplant is performed contralateral to facilitate surgical approach.

With infectious pathologies, mainly CF and bronchiectasis, the choice is always bipulmonary transplant [48]. Colonization by multiresistant germs which might be present in other pathologies usually also forces the choice of a bipulmonary transplant.

Primary PPH is a rare indication due to development of highly efficient drugs for its control [49]. The transplant of choice is usually bipulmonary transplant since it reduces the risk of posttransplant graft oedema. Dilation of the right ventricle with poor mobility with ultrasound and an ejection fraction below 20% may advise cardiopulmonary transplant. However, in many cases, right ventricle dysfunction improves after a bipulmonary transplant on normalization of preliminary pressures of the pulmonary artery [49]. In HPT secondary to heart defects, a bipulmonary transplant may be performed if it can simultaneously correct the heart defect and the heart is considered recoverable. It is true, however, according to international registry statistics, that bipulmonary transplant shows a slight but significantly better long-term survival [4].

Both transplant types are considered major thoracic surgery, and therefore require anaesthetic preparation with peculiarities typical of this kind of surgery, thus:

» Monitoring: ECG, SpO_2, femoral and radial arteries, a central port (usually internal jugular vein ipsilateral to lung transplanted) to which a Swan-Ganz catheter is attached, CO, SvO_2, $EtCO_2$, ventilation pressures, BIS, temperature, neuromuscular block, and a series of ABG.

» Intubation: use of selective intubation with double span tube (checking position with fibrobronchoscopy if necessary) and adjusting ventilation values (FiO_2, PEEP, respiratory frequency, tidal volume) according to pathology and patient condition. Baseline ABG is useful to control pCO_2 levels or permissive hypercapnia, which may reduce the incidence of barotrauma and haemodynamic alterations secondary to hyperinflation [50].

» Epidural analgesia: epidural catheter at T4-T6 level inserted prior to anaesthetic induction or after the surgical event. Several authors refer better pain control during the postoperative period, occasionally enabling early extubation with better incidence of complications related to hypoventilation, such as pneumonia or atelectasis, and a shorter ICU stay without relevant complications associated with the technique [51,52].

The requirement for ECC during the procedure depends on donor characteristics and the experience of each group. The decision may be taken before the intervention based on the patient's clinical history, like perfusion of the lung to be explanted or factors suggestive of HPT, or during surgery, this is why, above all in left-side single lung transplants, the surgical field should be prepared considering the possibility of peripheral cannulation. Patients with an ECMO system as a transplant bridge require special consideration, detailed below.

a) Approach

Standard posterolateral thoracotomy via 5th intercostal space is the most common approach for single lung transplant, although anterolateral thoracotomy without muscle section is a technique that enables an immediate postoperative improvement for patients (Figure 7).

Bipulmonary transplant is performed with very different incision types, such as transverse thoracosternotomy, bilateral anterolateral thoracotomy or bilateral anterior minithoracotomy.

Transverse thoracosternotomy via the 4th-5th intercostal space or clamshell is an excellent incision which, with muscle section of the lower pectoral end and partial separation of serratus, allows excellent access to the mediastinum, both vertices and diaphragms. This is why it is the incision of choice for clinical cases with complex surgery, especially those with intense adherences (bronchiectasis, silicosis, pleurodesis, etc.) [35]. Moreover, it facilitates ECC if required, and allows heart surgery where necessary. After opening the whole intercostal space, mammary vessels are dissected and ligated, and the sternum is transversally sectioned.

The pericardium can be widely opened in inverted T to facilitate an opening of the maximum incision without venous return problems due to stretching of the cavae. (photo)

A bilateral anterolateral thoracotomy with little muscle section is an incision that avoids section of the sternum and its possible complications, so some groups have adopted it as standard in less complex cases [35]. Mammary vessels can be ligated or dissected if 1cm of cartilage of the 4th parasternal costal arch is sectioned. This manoeuvre, together with intercostal musculature sectioning towards the paravertebral space, facilitates rib separation without rib fracture. There is generally good exposure of the aorta and atrium enabling commencement of ECC if necessary (Figure 8).

Medial sternotomy is used in cases requiring heart surgery associated with lung transplant. Some studies report a lower incidence of complications in bipulmonary transplants via medial sternotomy in comparison to those performed with clamshell [55].

b) Lung explant

Lung explant follows the technical principles of an intrapericardial pneumonectomy and is similar to a single or sequential twin lung transplant, although the view of the hila structures varies according to the surgical approach used.

2.3.2 Pulmonary hila dissection

After release of adherences and triangular ligament section, the main pulmonary artery is dissected, surrounded by a tape and clamped with tourniquet to evaluate right ventricle response to clamping, and therefore haemodynamic tolerance to the pneumonectomy and the possible need for ECC. It may be declamped again so that the heart is not subjected to prolonged effort and to facilitate dissection of the arterial branches, or it may be totally or partially obstructed if the vascular shunt created does not allow maintenance of correct oxygenation. The pericardium is opened wide in front of the pulmonary veins which are dissected in the intra-extra-pericardial space.

The first branch of the pulmonary artery is dissected at a minimum. During hilum dissection it is very important to identify the phrenic nerve route, taking constant care not to damage it because it is essential for patient respiratory function. Particular care is required in bipulmonary transplants.

2.3.3 Pneumonectomy execution

Vascular structures are dissected as distally as possible, generally using mechanical suture devices, although sectioning between ligatures is possible. It is preferable to section the artery first to prevent lung hepatisation and loss of blood accumulated in the surgical part.

Dissect the bronchus and aspirate prior to sectioning next to the lobular bifurcation. The lung is only held by fat, lymph vessels and peribronchial vessels, which should be sectioned prior to sealing or with ligature of all the structures via electrocoagulation, silk ligatures, metal clips or auto-sutures.

The lung is removed, and the pulmonary hilum prepared for implant, completing the posterior pericardial section to release the left atrium and allow deep atrial clamping. Dissect the intra-extra-pericardial arterial stump, taking care not to damage the nerve travelling through the left hemithorax. Next, cut the bronchus leaving it uniform, well-vascularized, with approximately one ring free for suture, and with the redundant slightly membranous portion. Perform meticulous haemostasis of the entire hilum, since it will be difficult to correct bleeding there once sutured.

c) Lung implant

2.3.4 Bronchial suture

Prior to declamping the pulmonary artery, as part of immunosuppression induction, administer 1 gramme of methylprednisolone (divided into 2 bolus of 0.5 grammes in the case of a bipulmonary transplant).

Place the patient in Trendelenburg position and declamp the atrium to reperfuse the lung in retrograde direction and let the air out along with the rest of the reperfusion liquid via the last stitch of the arterial suture prior to knotting.

Knot the arterial suture, and then very slowly declamp the artery to prevent a brusque increase in pressure in the donor lung vascular bed, which is cold and under the effects of ischaemia that might favour an onset of reperfusion problems, especially if systolic pressure is raised at the time.

Fibrobronchoscopy should be performed at the end of the intervention to check the condition of the bronchial suture and clean the bronchial tree of secretions. In addition, take a sample of bronchoaspiration for culture.

2.3.5 Atrial suture

Vascular sutures may commence at the artery or atrium. As venous suture may present greater difficulties, it is advisable to start with the atrial suture, at least in the case of a small thorax or with deep venous bifurcation.

A triangular clip is placed on each venous stump, and it may even be necessary to place a clip between both veins. To traction both, place a Satinsky-type clamp on the atrium, as centrally as possible, without causing haemodynamic problems. On the right side, it may occasionally be necessary to dissect the interatrial space. Cut back the veins following the proximal part of the ligatures, and section the existing space between both veins. Perform continuous suture of the atrium with 1 or 2 stitches of non-reabsorbing monofilament 5-0 (usually Prolene®).

2.3.6 Arterial suture

Prior to declamping the pulmonary artery, as part of immunosuppression induction, administer 1 g of methylprednisolone (divided into 2 bolus of 0.5 g in the case of bipulmonary transplant).

Place the patient in Trendelenburg position and declamp the atrium to reperfuse the lung in retrograde direction and let the air out along with the rest of the reperfusion liquid via the last stitch of the arterial suture prior to knotting.

Knot the arterial suture, and then very slowly declamp the artery to prevent a brusque increase in pressure in the donor lung vascular bed, which is cold and under the effects of ischaemia, which might favour the onset of reperfusion problems, especially if systolic pressure is raised at the time.

2.3.7 Bronchoscopic control

Fibrobronchoscopy should be performed at the end of the intervention to check the condition of the bronchial suture and clean the bronchial tree of secretions. In addition, take a sample of bronchoaspiration for culture.

2.4 ECMO

An extracorporeal membrane oxygenation (ECMO) or extracorporeal life support (ECLS) system is a circulatory and/or respiratory support measure that enables correct maintenance of oxygenation and perfusion both for waiting list patients presenting a clear worsening of respiratory function and during lung transplant or the postoperative period.

An ECMO circuit comprises a series of cannulas and lines connecting a centrifuge pump and membrane oxygenator with each other and with the patient, to pump and oxygenate the patient's blood.

The different ECMO system therapies performed are:

- venoarterial ECMO (VA ECLS): cardiopulmonary support;
- venovenous ECMO (VV ECLS): respiratory support;
- elimination of CO2 (rCO2): "ventilation support".

Venovenous ECMO is the system most commonly used in lung transplants although in other cases, RV deterioration associated in some patients to HPT may be optimized with a venoarterial ECMO. Depending on cannula placement, the ECMO will have a peripheral or central implantation.

The indication for ECMO posttransplant is clearly established, in most cases as a bridge to graft recovery after the onset of primary failure within the first hours [58,59]. However, its use on waiting list patients with a worsening function who do not respond to maximum ventilation support measures is debatable,

because these are patients whose delicate clinical situation is determined by worse results and considerable mortality, particularly during the first year.

Certainly, bearing in mind the results of some published studies, this seems to be another option for waiting list patients as a bridge gap to an organ [60,61]. Furthermore, ECMO may be a valid alternative to facilitate oxygenation and the necessary haemodynamic support during the surgical procedure, avoiding use of ECC and with a lower incidence rate of pulmonary and renal complications [62].

2.5 Surgical complications

Bronchial suture complications

Bronchial suture complications were the main cause of short-term mortality, and the main limiting factor before the clinical development of lung transplantation [63] since lung transplant is the only solid organ transplant where original graft circulation is not re-established. Today bronchial complications have greatly diminished due to better preservation, surgical techniques and post-operative patient management. Thus, from an initial incidence of 60-80%, most authors today report an incidence of 10-15% with mortality between 2-3% [64].

A review by the Cordoba group, which analysed 343 bronchial sutures, found 31 airway complications in 27 patients: 22 cases of stenosis, 5 dehiscence and 4 malacia. Surgical technique with/without telescoping showed no differences, whereas bipulmonary transplant, airway colonization and prolonged intubation were factors related to the presence of complications during follow-up. The paper concluded that endoscopic and surgical treatment currently resolve most of these complications, with mortality at 1% [65].

Dehiscence

A rare and very serious complication. If it spreads, it might be related to mediastinitis, pneumothorax, haemorrhage due to broncho-arterial fistulae and death. Depending on size, treatment should be conservative, reducing the dose of corticosteroid treatment as far as possible, with insertion of thoracic drainage to drain the pneumothorax generally associated with this, attempting early extubation of the patient, keeping the airway free from secretions, and with accurate antibiotic cover [49]. An intermediate solution would be placement of a prosthesis as support to facilitate the growth of granulation tissue. Lastly, there is the surgical option [66], at times prior to dehiscence and in other cases as a separate body showing necrotic plaques at suture level, which may propitiate fungal colonization.

Stenosis

This is the most common airway complication. Its aetiology is similar to the causes of dehiscence and one of the many responsible factors is ischaemia. Its frequency is approximately 4-24% according to different series [49]. It may consist of fibrotic tissue, granulomas or stenosis malacia secondary to bronchial wall weakness. The onset is usually silent, with a drop in spirometry values or exercise tolerance, or with bouts of pneumonia or purulent bronchitis.

Diagnosis may be by CT, but a subsequent bronchoscopy is the test necessary for confirmation.

Treatment is endoscopic with laser (YAG laser or argon plasma coagulation) and balloon dilations, or with rigid bronchoscopy. The incidence of recurrence is frequent and occasionally requires placement of a stent. Most groups present results after inserting self-expandable metal stents [67], which have the advantage of easy insertion with flexible bronchoscopy and fluoroscopy. The main hurdle is the difficulty in removing it after 1-2 months and the onset of granulomas. Silicone stents require rigid bronchoscopy and general anaesthesia for insertion but have the advantage of easy removal during follow-up. Dilation prior to insertion is required since they are not flexible [68]. In recent years, some groups have indicated reabsorbing prosthesis for patients with stenosis malacia. These devices have less radial strength than

the previous ones but have the inherent advantage of being reabsorbing. Studies are still required on these to confirm their long-term efficacy.

Pleural cavity complications

Generally related to a complex procedures like intense adherences or difficult dissections during implant. The most frequent onset is of residual air chambers or post-surgical haemothorax (usually associated with intense adherences or use of ECC). Occasionally re-intervention is required during the first hours, but this is not related to any significant increase in post-operation mortality [69].

Vascular complications

The incidence occurs in 1.75% of anastomosis during posttransplant, and morbidity and mortality is high [70]. Early diagnosis will enable survival of this patient subgroup. The most frequent causes are vessel calibre difference between the donor and recipient, technical difficulties and the onset of clots. It should generally be suspected in patients with hypoxia-instability or HPT data.

Pulmonary vein stenosis shows up in the imaging tests associated oedema at parenchyma level corresponding to that venous territory. Treatment type will generally be determined by the patient's clinical situation, organ viability and time since transplant [71]. If findings are intraoperative, during execution of re-anastomosis, the commencement of ECC is necessary if it has not already begun. Detection during the first hours with infarction factors or, on occasion, lung damage requires resection of the affected parenchyma or even a retransplant.

Interventional treatment via percutaneous angioplasty with/without posterior stent placement has proven to be a safe procedure with good results in patients with stenosis who do not have associated lung damage [72]. We must not forget the possibilities of migration, re-stenosis, thrombosis and embolization associated with this procedure [73].

Surgical wound complications

Lung transplant patients receive high doses of corticosteroids during the first weeks posttransplant. Thus, the incidence of total or partial of dehiscence of the surgical wound is not infrequent. This should be reviewed periodically to optimize early surgical repair of the defect if necessary.

CONCLUSIONS

» In lung transplantation, a standardized donor lung evaluation is particularly important in order to maximize peri- and post operative success. For further information, see ISHLT data about the number of transplants.

» Particularly in lung transplantation, the number of transplants performed each year has a direct impact on the outcome of transplantation.

» It is important to measure and evaluate certain donor parameters and conduct a with a macroscopic evaluation. A donor bronchoscopy is less and less frequent, and DCD donors are increasingly used in lung transplantation.

» The recipient transplantation procedure needs to be performed in a well-experienced centre, with well-developed intensive care and experienced lung and cardiac surgery team.

» Surgical complications are mostly seen in relation to the bronchial anastomosis and the comorbidity factors of extra corporal circulation. Particularly in case of any acute complications in the recipient, the framework of a multi-disciplinary thoracic heart and lung department, the possibilities of ECMO and intensive care are necessary.

[See bibliography for this unit at the end of topic 6]

TOPIC 6 - Unit 3

Postoperative management and medical follow-up (early/late & histopathology/ radiology)

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INTRODUCTION

Careful short and long-term follow-up of the transplanted patient are essential for good results. Thanks to new immunosuppressants and prophylactic guidelines, in addition to better physiopathological knowledge of the different types of rejection, we have achieved a slow but progressive improvement in survival rates. However, today, mean graft life continues to be slightly less than that of other solid organ transplants.

According to ISHLT data, 90-day survival is 88%, 1-year survival 80% and 5-year survival 53% for patients transplanted between June 1990 and June 2012 [4]. Furthermore, patients surviving year one present an average survival rate of 7.9 years. Transplant type, base disease, and the onset of complications may increase or decrease this prognosis. Likewise, for instance, the average survival rate for a CF patient receiving a bipulmonary transplant is over 11 years.

Therefore, a good progression partly depends on early prevention and the diagnosis of possible complications, and we will comment in detail on the diagnosis and treatment of different kinds of rejection, infections and the development of neoplasms secondary to immunosuppressive treatment. Finally, we look at immunosuppressive treatment guidelines and controls during follow-up.

1. POSTOPERATIVE MANAGEMENT

Both during early-stage follow-up and later, the aim is to seek a balance between the need for immunosuppression in a transplanted patient to prevent rejection while administering the minimum dose necessary to minimize the side effects of immunosuppression treatment, which favour infections and the development of tumours. Organ requirements may vary depending on the patient and stage of transplant follow-up.

Therefore, during the postoperative period, we must consider the recipient's prior situation, base disease, intraoperative incidents, donor and transplant type.

During the first day, the patient is usually in recovery or in the ICU while they require respiratory or haemodynamic support. The aim is early extubation of the patient if this was not possible in the operating theatre, provided the different blood gas levels and patient respiratory mechanics allow. This favours early patient mobilization, facilitating the possibility expelling secretions, thus avoiding one of the main complications for a lung transplant patient: the onset of respiratory infections.

Therefore, the patient should initially be monitored with same parameters as in the operating room: ECG, SaO_2, capnography, temperature, hourly diuresis and balance/shift, serial ABG and glycaemia, and haemodynamic parameters. Moreover, chest drainage must be evaluated, chest X-rays taken, analysis with haemogram, biochemistry and clotting on arrival and daily monitoring of immunosuppressive drugs.

During the patient's stay in recovery, respiratory isolation and contact protection must be maintained, with a specifically designed transplant protocol (use of mask, gloves, cap, coat and strict hand washing), with specific emphasis on respiratory physiotherapy.

Oral food intake should restart early, on patient extubation, and correct intestinal motility should be verified.

For patients with difficulties in extubation who do not have life-threatening complications, a premature tracheostomy is performed (in week 1) to advance in weaning, keeping the patient awake and more active, giving greater facility to aspirate secretions and promote the progressive removal of respiratory assistance.

Likewise, during this period, the necessary bronchoscopies should be performed to aspirate secretions or take samples for cultures for suspected respiratory infections. We must remember that the transplanted lung is a denervated organ, as both afferent and efferent branches are sectioned during surgery. This alters the response to hypercapnia, cough reflex and mucociliary clearance [74].

During the post-operative period we must rule out possible premature or late surgical complications, including haemorrhage, prolonged air leakage, bronchial or vascular anastomosis problems, etc. We should also be alert to possible medical complications, chiefly primary lung graft failure, infections, acute rejection and digestive system complications.

1.1 Complications

Primary graft dysfunction

Primary graft dysfunction (PGD) is graft failure within the first 72 hours, generally accompanied by non-cardiogenic pulmonary oedema and an absence of any other cause justifying the symptoms [75]. Therefore, we must rule out the following circumstances:

- Pulmonary oedema of cardiogenic origin.
- Suspected rejection. As PGD onset occurs during first 72 hours differential diagnosis is performed with hyperacute rejection due to preformed antibodies.
- Pneumonia: presence of fever, leucocytosis, purulent secretions or positive cultures in the bronchoscopy.

» Venous anastomosis abnormalities: a transoesophageal echocardiogram, CT angiography or arteriography performed previously in accordance with the patient's clinical situation.

» Hyperinflation of native lung in COPD patients after a single lung transplant.

The onset of PGD is considered a risk factor for early death, multiplying the risk of demise by 8 at 90 days in severe cases [76]. Likewise, a negative impact on long-term survival has been described, with a greater incidence of BOS in patients with grade 3 PGD.

The causes are not well-established, although an important role is given to damage secondary to graft ischaemia and reperfusion. Other donor-related risk factors are those associated with damage secondary to brain death in the lung donor, elderly donors, low P/F ratio or smokers (over 20 packets/year). Some reports exist of a relationship with the events of the surgery itself, the need for ECC, complicated surgery, haemorrhage, etc. From the recipient viewpoint, the presence of PTH or interstitial pulmonary disease diagnosis increases the risk of PGD [77].

The conclusions of a recent meta-analysis that included data from 13 studies and analysed 10,042 lung transplants found that the data to consider as recipient risk factors are: female, African or American, prior diagnosis of idiopathic pulmonary fibrosis, sarcoidosis or PPHT, and the use of ECC or blood derivatives [78].

Depending on the degree of organ involvement, the ISHLT has defined the following grades of PGD [79]:

» Grade 1: infiltration in chest X-ray with P/F ratio higher than 300.

» Grade 2: infiltration in chest X-ray with P/F ratio between 300-200.

» Grade 3: infiltration in chest X-ray with P/F ratio under 200. Any patient requiring the use of oxygenation via ECMO or mechanical ventilation with FiO_2 higher than 0.5 and the need for nitric oxide past 48 hours posttransplant.

Faced with several different blood oxygen values the worst value must be used as reference to classify the PGD.

The incidence reported varies depending on series, but ranges between 15 and 25% [80].

Treatment options depend on grade of PGD and the patient's clinical situation, i.e., an increase in mechanical ventilation associated with negative balances and the use of pulmonary vasodilators (prostaglandins and inhaled nitric oxide). Today, the use of ECMO in patients with grade 3 primary failure is clearly established.

Infection

1) Bacterial infection

A cause of premature and late mortality in transplanted patients, with the greatest risk of bacterial pneumonia presenting in the first month. During the first days posttransplant, we must consider germ transmission from lung donors. For this reason, protocol dictates cultures be taken during extraction or bench surgery. However, the most serious risks are frequently found in the recipient due to previous colonization, immunosuppressive drugs, prolonged mechanical ventilation, pain and denervation of postoperative cough reflex, which hinders the possibility of expelling secretions, etc. Likewise, we must consider direct contact of the transplanted organ with the exterior.

The possible severity of the onset of pneumonia in an immunosuppressed patient during the first posttransplant days/weeks, and the high percentage of patients who will suffer an episode of bacterial infection during follow-up (35-65%) leads to the need for antibacterial prophylaxis [81].

Antibacterial prophylaxis should be aimed at covering the most common micro-organisms in patients under the circumstances, the most common of which is *P. Aeruginosa* followed by *Staphylococcus aureus* [82]. For patients with negative cultures, not colonized patients and those who have no other risk factor, the prophylaxis varies from centre to centre, but usually includes a third-generation cephalosporin, piperacillin-tazobactam or carbapenem. Duration of treatment depends on donor/recipient culture results but should be at least 2 weeks for negative results. When deciding on appropriate treatment and duration both donor and recipient risk factors must be considered [83].

For positive cultures prior to transplant, prophylaxis must be aimed according to the previous antibiogram. Patients with CF and bronchiectasis, with multiple antibiotic cycles prior to transplant due to over-infection, include the germ selection with serious antibiotic resistance, particularly: *Pseudomonas* multi-resistant (*Ps. Morphotype mucoid, Stenotrophomonas maltophilia, Burkholderia cepacia, Alcaligenes xylosoxidans*) and Methicillin-resistant *Staphylococcus aureus* (MRSA).

Regarding pseudomonas, a third-generation cephalosporin (piperacillin-tazobactam or ceftazidime) or meropenem-imipenem with quinolone (ciprofloxacin or levofloxacin) or aminoglycoside (tobramycin or amikacin) is usually prescribed. In cases that are resistant to these, cotrimoxazole or colistin can be used.

MRSA is generally treated with linezolid or vancomycin. Treatment will be maintained for 2-3 weeks post-transplant depending on patient progression and posttransplant cultures, particularly those of bronchial aspirate obtained via bronchoscopy [83].

In most centres this systemic prophylaxis is accompanied by inhaled antibacterial prophylaxis [83], generally with tobramycin (100 mg/12 hours) administered to all patients post-extubation. In patients who are allergic, intolerant or resistant to a tobramycin use colistin (1 million UI/12 hours). This prophylaxis is maintained during the first 3 months posttransplant and prolonged to 6 months in patients colonized by important germs, who were transplanted due to a septic pathology or high immunosuppression due to episodes of acute rejection.

2) Viral infection

This refers mainly to cytomegalovirus (CMV), the opportunist infection that is most frequent during follow-up, which occurs in 20-50 % of patients after suspension of prophylaxis depending on series [84].

This virus has an immunomodulation effect, and CMV infection has been described as an acute/chronic risk factor [85]. It increases the risk of associated opportunist infections and the development of tumours [86]. Consequently, its effects vary from inflammation to increased morbidity and reduced graft and patient survival.

The first-year posttransplant is the period with greatest incidence of reactivation, with effects that may be both direct (CMV infection or disease) and indirect (opportunist infections, tumours, bronchiolitis).

We distinguish CMV infection as the asymptomatic replication of the virus, and CMV disease as replications associated with symptoms, like a typical viral syndrome with fever, malaise, leucopoenia, thrombocytopenia or tissue invasion with dysfunction of the affected organ, most frequently the lung, intestine or central nervous system [87].

There is wide consensus among groups that prophylaxis in initial periods with high doses of immunosuppression is very beneficial, preventing virus reactivation both in the periods with biggest risk of disease, during treatment of an acute rejection episode and when there is an increase in immunosuppression levels [88].

The scientific community is divided regarding the prevention of CMV disease and the effects of indirect virus, universal prophylaxis and pre-emptive therapy, which would be monitoring of viral replication and early treatment. Most centres favour using universal prophylaxis at commencement, subsequently associated with PCR control of CMV levels in blood during follow-up, a combination of both strategies [89].

We need to identify risk subgroups, so serology for donor virus (D) and recipient (R) is the most important factor to consider. Thus, the D+R- serology is the most important risk factor for disease development. Likewise, D-R- serology is the lowest risk. Other factors to consider are the use of induction treatment, type of immunosuppressant used, situations of intercurrent infection by another germ or rejection episodes, as well as recipient age [87].

Some groups use prophylaxis with IV ganciclovir at 3-5 mg/kg/12 hours until day 14 [90], adjusting the dose to kidney function from estimated glomerular filtration. In cases with a CMV donor-recipient concordance D+/R+, D-/R- and D-/R+ this starts on day 5 posttransplant. In D+/R- cases (greatest risk) it starts within the first 24 hours posttransplant.

On day 15, or in some groups on commencement of oral tolerance, ganciclovir is replaced with oral valganciclovir at 900 mg/24 hours. Again, it is adjusted to kidney function.

The main side effects of both treatments are kidney failure and medullar aplasia, particularly leucopoenia. Occasionally, side effects force the suspension of prophylaxis after an evaluation of the risk-benefits of maintaining this treatment. In these cases, CMV PCR is monitored weekly during the first weeks.

The duration of prophylaxis is not well-established. If we review the literature, some groups defend prolonged and even indefinite prophylaxis whereas others propose an intermediate approach between the former and those who solely administer preventive therapy. The main limitation of those in favour of prolonged universal prophylaxis is the onset of the side effects of valganciclovir, generation of resistance to ganciclovir, and cost [91].

The recommendations for valganciclovir prophylaxis for lung transplant patients is at least the first 3-6 months, except in the case of kidney toxicity or leucopoenia. The current tendency is to prolong it as long as possible, up to 6 months posttransplant, particularly in patients with a high risk of immunosuppression, a history of acute rejection and D+R- serology [92].

3) Fungal infection

Although fungal infections are less frequent posttransplant, their incidence is between 15 and 35% [93]. The most common germs are *Candida* and *Aspergillus*, which are typically found in the first 6 months posttransplant. We must distinguish between colonization, which is common in CF and COPD patients in the native lung [94], and invasive disease by these germs. The onset of invasive *Aspergillus* is estimated at 5% in transplanted patients during first year and associated with serious mortality [95]. Prophylaxis aims to not only avoid colonization but also to prevent tissue invasion in colonized patients with greater immunosuppression. Likewise, the presence of fungi manifests in many cultures of patients presenting complications in bronchial anastomosis [96].

Prophylaxis is therefore justified, given the seriousness and high mortality of this type of infection, and includes fluconazole at 200 mg/12 hours from transplant to day 21 in order to essentially prevent candidemia in patients with multiple ports and also candidiasis mucosa. Treatment will be prolonged over time depending on the situation of each patient. On suspension of fluconazole, it is essential to closely monitor immunosuppressive plasma levels, given the intense interaction of azoles in anticalcineurinic metabolism, since plasma levels may drop as much as 50% even without dose modification, and this is a period when there is a high risk of acute rejection.

In patients with positive pretransplant cultures for fungi of the *Aspergillus* genre, fluconazole is replaced with itraconazole at 200 mg/12 hours for 3 months, controlling cyclosporine or tacrolimus levels after their suspension, since interaction with these is even more intense.

We can also use voriconazole, although given its greater toxicity (particularly hepatic), it is preferable to reserve it for treatment of *Aspergillus*, establishing it when positive cultures exist posttransplant [97]. Begin with a dose at 400 mg/12 hours on day one, continuing with 200 mg/12 hours.

As already mentioned, the airway is the frequent location of these germs, so most of the guidelines currently recommend inhaled liposomal amphotericin complex [98]. This starts for 3 months in patients with positive cultures for fungi, particularly *Aspergillus*, or high-risk patients for whom it may be prolonged 6-12 months.

The use of prophylaxis during pretransplant with inhaled amphotericin in colonized patients and during the first days has significantly reduced the incidence of fungal infection.

Pneumocystis jirovecii

Pneumocystis jirovecii infection is a very serious process which may appear in immunosuppressed patients, such as lung transplant recipients, due to maintained immunosuppression to prevent rejection. The greatest posttransplant risk is during the first 6 months of follow-up [99]. Currently the incidence in different series is almost zero [100]. Thus, the results presented by the RESITRA study [90] analysing the incidence of pneumonia in a group of 236 transplants performed between 2003 and 2005 by all the Spanish groups, found no presentations of pneumonia episodes during the study period for that aetiology due to the universal prophylaxis anti *Pneumocystis jirovecii*.

Treatment is with sulfamethoxazole and trimethoprim (160 mg-800 mg) at 1 tablet/48 hours, starting on day 21 posttransplant. This is a generally well-tolerated prophylaxis with few side effects, so although it is generally maintained until the end of months 6-9. Some groups consider the possibility of prolonging this period [101]. Treatment is usually reinitiated in patients that require an increase in or maintenance of elevated immunosuppression levels due to chronic rejection.

The convenience of maintaining this prophylaxis and its duration will be evaluated in kidney failure patients.

Gastrointestinal alterations

Given their frequency in this type of patient, especially during the first days posttransplant, and the associated morbidity and mortality, we devote a separate section considering the most frequent complications.

On the one hand, we must bear in mind gastroparesis, associated with irritation of the vagus nerve during surgery, dehydration due to the initial tendency to maintain negative balances in order to prevent pulmonary oedema during the early days, and medication (especially immunosuppressive drugs). This condition is characterized by slow gastric evacuation with supraumbilical distension after meals, a sensation of fullness or even nausea and vomiting. It is improved and treated with metoclopramide due to its anti-emetic and pro-kinetic action, or with pro-kinetic cinitapride without anti-dopamine action, therefore with an anti-emetic effect. If the patient has a history of hiatus hernia with gastroesophageal reflux, treat with domperidone.

Constipation problems are associated with an initial lack of patient movement, brusque changes in life habits, and dehydration due to strict hydric balance to prevent oedema, reduced food intake and epidural analgesia. Treat with lactitol in powder in 10 g sachets, laxative solution or others.

Both gastroparesis and constipation are frequent problems that generate not only discomfort for postoperative patients but are also frequently associated with breathing difficulty and secondary atelectasis, possible respiratory infections, impaired absorption of different foods or treatments with the resulting problems to achieve therapeutic levels in blood, which may lead to oral intolerance or ultimately to more serious digestive complications as detailed below.

A severe digestive complication is understood as one with serious associated morbidity and mortality that may occasionally require aggressive procedures, e.g., acute cholecystitis, intestinal perforation, ulcers, intestinal occlusions, mesenteric ischaemia and pancreatitis. Lahon B et al. analysed the incidence of these events during the first 30 days of follow-up in lung transplant patients, reporting an incidence in 351 patients, 7.4%, with a direct mortality of 19% [102].

Acute rejection

This is one of the most frequent complications of lung transplant. Its incidence is usually around 30%, according to ISHLT data [4], although some groups report 75% after transbronchial biopsy [103]. Its incidence is greater in the first 3 months and particularly during the first 2 weeks, although it may occur at any time in the recipient's life, causing up to 20% of late acute rejections after year one.

There is usually a clinical diagnosis where the main indication is respiratory worsening of patient. It may also appear with dyspnoea, cough, general malaise, fever, leucocytosis, tachycardia, and an increase in pleural drainage, followed in the short-term by the onset of perihilar infiltration and pleural effusion in the chest X-ray. Its clinical expression is quite non-specific presenting a differential diagnosis with other processes, especially infections.

Its symptoms may be so subtle that the patient simply refers asthenia or restlessness with worsening of baseline O_2 saturation compared to previous days, and in 40% of cases manifestation is silent [103]. Co-existence of low cyclosporine or tacrolimus levels supports diagnosis.

The gold standard diagnosis is a transbronchial biopsy, which shows the presence of lymphocyte infiltration at perivascular level, and in serious cases even at interstitial level. Lymphocytic bronchiolitis may be associated [49].

According to the Lung Rejection Study Group (2007) [104], acute rejection is classified in accordance with transbronchial biopsy findings:

- **GRADE A0:** no evidence of infiltration.
- **GRADE A1 (minimal):** perivascular lymphoid infiltration, found with difficulty with little magnification.
- **GRADE A2 (slight):** frequent lymphoid, eosinophil and plasmatic infiltration.
- **GRADE A3 (moderate):** infiltrates interstitial septal alveoli.
- **GRADE A4 (severe):** diffuse interstitial infiltrates with diffuse alveolar damage, haemorrhage and/or parenchymal necrosis.

A. Bronchial inflammation/Lymphocytic bronchiolitis

- **GRADE BX:** non-evaluable.
- **GRADE B0:** no inflammation.
- **GRADE B1:** lymphocytes rarely in submucosa.
- **GRADE B2:** circumferential lymphocyte bands without epithelial inflammation or necrosis.
- **GRADE B3:** circumferential lymphocyte bands with epithelial inflammation or necrosis.
- **GRADE B4:** circumferential lymphocyte bands with epithelial inflammation, ulceration and necrosis.

There is evidence of a second type of acute rejection in which the humoral component plays an important role mediated by specific anti-HLA antibodies, which develop posttransplant and whose clinical expression is similar to the previously described cellular rejection [105,106]. In this case, the diagnosis criteria are [107]:

- presence of donor-specific anti-HLA antibodies;
- evidence of capillaritis in histopathological study;
- Cd4 deposit at endothelial level;
- organ dysfunction.

Treatment must be early, with methylprednisolone bolus 500 mg/12 hours during 3 days with a progressive decrease. Antibiotic, anti-CMV and antifungal prophylaxis must be established as must controlled isolation measures. To obtain a good response to corticosteroids it is essential to maintain the correct levels of immunosuppression.

Correct response to this treatment enables confirmation of clinical diagnosis of acute rejection. Generally, resolution of symptoms, improved lung function and radiological normalization are evident with the first doses of corticosteroid. Although rarely fatal, it has been related as a risk factor in the development of chronic rejection, hence the tendency to initiate treatment even in patients with low-level or asymptomatic rejection [108].

In humoral rejection, 50% of cases do not respond to corticosteroid treatment, so occasionally plasmapheresis 105, or intravenous immunoglobulin and anti-CD20 monoclonal antibodies must be associated [106].

2. MEDICAL FOLLOW-UP

Once the postoperative period has ended, the aim is to prevent and treat complications derived from immunosuppression treatment, chiefly tumours and infections, as well as to prevent and initiate early treatment of late graft dysfunction to provide the transplanted patient with survival and quality of life.

During initial postoperative period, the main causes of death are primary graft failure and non-CMV infections. Until year one, non-CMV infections continue to be the most frequent cause of death. After year one, chronic rejection becomes the permanent first cause of death. The incidence of neoplasms increases in the long term (5-10 years) and another consideration is comorbidity due to the effects of medical complications associated with the transplant, the majority of which are related to prolonged immunosuppression.

Thanks to new immunosuppression treatment protocols and research lines, survival has increased notably in recent years.

2.1 Complications

Infections

Infections represent 35% of first year deaths [90] and are the main cause of death during that period. The pathogenesis of chronic rejection likewise plays a major role [49], hence the importance of prophylaxis and early treatment. The most common presentation is pneumonia.

During the postoperative period and early posttransplant months, bacterial infections are the most common, presenting in over 50-60% [109] of cases. This is due to high immunosuppression levels, previous donor-recipient colonization and the direct contact of the transplanted organ with the exterior. The most common germs are Gram-negative [49], chiefly *P. Aeruginosa, Staphylococcus aureus* and *Haemophilus influenzae.*

When diagnosing, we must consider clinical-radiological and microbiological criteria. Given the seriousness, treatment must commence empirically in the face of suspected diagnosis, taking into account the patient's prior cultures. After isolation, the germ treatment should be adjusted to the antibiogram result. In the event of a bad response to the prescribed treatment and an absence of cultures, a bronchoscopy is performed to obtain selective bronchoaspiration (SBA) and bronchoalveolar lavage (BAL) for culture if the patient's respiratory situation allows. For serious infections, wide spectrum antibiotics are recommended to cover Gram-negative and Gram-positive germs.

With bacterial infection, correct adjustment of immunosuppression levels is essential, and in serious cases this treatment may even be reduced.

Fungal infections appear in 15-35% [110] of cases and involve greater mortality. The onset is later, from month 6, due to maintenance of long-term inhaled prophylaxis with amphotericin liposomal.

Problems related with anastomosis like stenosis or necrosis appear as the appropriate substrate for fungal colonization-infection. Other risk factors are the immunomodulation effect of co-existing infections, neutropenia, donor-recipient transmission [111] and native lung colonization in single lung transplants. Colonization is more common in patients with CF and COPD. A relation has also been established between this germ type and patients with chronic graft dysfunction [112]. Not all colonized patients present invasive disease.

The most common forms are: *Candida* and *Aspergillus* species, whereas *Zygomycetes, Scedosporium, Fusarium, Cryptococcus* species, histoplasmosis and coccidiomycosis are less common [83].

For the diagnosis of fungal infection, the existence of a positive culture is essential, whether of sputum or SBA. A positive culture for fungi may be a colonization, tracheobronchitis or invasive fungal infection depending on the patient's clinical and radiological signs.

The *Aspergillus* species is most frequently related with tissue invasion, with positive cultures in most colonization, and less than 10% of these patients develop the invasive disease, although there is high mortality among those that do [113].

With a suspected diagnosis of invasive disease, the patient's symptoms must be considered (fever, bloody sputum, dyspnoea) associated with a positive culture, radiological data (consolidations, nodules, cavitary lesions and mass-like opacities, often with a halo sign) and analysis (galactomannan [114], PCR [115] and 1, 3-β-D-glucan [116]) taking into account that a precise diagnosis is established by biopsy showing tissue invasion.

Considering its seriousness, in the face of several cultures that are positive for *Aspergillus* in a patient who is occasionally symptomatic or has few symptoms or even without radiological findings, treatment is preferred.

The treatment of choice would be voriconazole [117] associated with inhaled amphotericin liposomal (50 mg/weekly) and a reduction in immunosuppression if possible. The average time depends on patient symptoms and the results of subsequent cultures, although generally these patients are recommended prolonged treatment between 3 and 12 months if the side effects (chiefly hepatoxicity) allow it. Inhaled treatment to be maintained long-term as prophylaxis.

We must remember the intense interference of voriconazole with cyclosporine and tacrolimus levels, which forces the dose of these to be reduced by half or one third with close control of their levels.

The *Candida fungus* is the second most frequent cause of invasive fungal infection posttransplant, with its presentation being unusual, since positive cultures mostly represent colonization [118]. It appears most frequently in first 4 weeks, generally with patients in recovery/ICU. Analytical, clinical and bronchoscopy data will present the differential diagnosis for this disease and the corresponding treatment.

For *Candida albicans* infections, the treatment of choice is fluconazole or echinocandins. In serious cases or resistant strains, the use of amphotericin B is considered. Treatment duration depends on seriousness and response but is never less than 2 weeks [118].

Among viral infections, CMV is the most important. Its frequency and seriousness have greatly reduced with systemic universal prophylaxis using valganciclovir. Although its mortality is low, its immunomodulation effect means CMV infection is one of the main risk factors for acute rejection and long-term chronic rejection [85]. This has led to a prolongation of posttransplant prophylaxis to month 6, except for toxicity (chiefly kidney failure or leucopoenia) in young patients and in cases of CMV donor+/recipient- concordance or high range immunosuppression due to prior acute rejection episodes.

Performing CMV PCR plays a very important role in CMV infection prevention, provided the patient undergoes a control analysis at check-ups. In this, CMV infection can be detected in patients who are still asymptomatic. In these cases, treatment is with oral valganciclovir [89] 900 mg/12 hours (or kidney func-

tion adjusted dose) until PCR is negative, continuing with secondary prophylaxis in most protocols of 900 mg/24 hours for a further 4 weeks [89]. A PCR control will also be performed 2-4 weeks after treatment completion, with subsequent routine controls at each check-up.

CMV disease is when PCR positivity is added to specific organ symptoms. The most common involvement is pulmonary with fever, general malaise, dyspnoea, cough and diffuse interstitial infiltration in the chest X-ray. It is also the most frequent form in patients with CMV donor+/recipient- concordance and may cause serious pneumonitis with respiratory failure and the need for mechanical ventilation if not treated promptly. It may also cause more or less severe gastritis, colitis, gastroenteritis, hepatitis, or simply pseudo-flu symptoms with long bedrest [87].

Although in mild cases the use of valganciclovir as a therapeutic agent has proven useful, the drug that shows effectiveness in series forms is IV. ganciclovir 5 mg/kg/12 hours, or kidney function-adjusted dose. It is important to perform a creatinine clearance test prior to commencement of treatment for better dose adjustment until clinical resolution and 2 consecutive, negative CMV PCR (weekly). Some groups recommend adding specific IV gamma globulin [119] then continuing a further 4-8 weeks with oral valganciclovir. In the event of bad response or resistance to ganciclovir, treat with foscarnet (90-120 mg/kg/12 hours) [89].

A herpes zoster infection with skin lesion is treatable with oral famciclovir 750 mg/24 hours 7-10 days. In cases of extensive involvement or chickenpox treat with IV acyclovir [120] 5 mg/kg/8 hours 7-10 days.

Epstein–Barr virus infection has been related with the onset of posttransplant lymphoproliferative disease [121], particularly in patients with negative pretransplant serology which subsequently turns positive, although the appropriateness of antiviral treatment in these cases is debatable.

Respiratory virus infections affect a large percentage of lung transplant patients during follow-up, their order of frequency being rhinovirus, parainfluenza, coronavirus, influenza, metapneumovirus and respiratory syncytial virus (RSV) [122]. Some studies report a relation between this viral group and the onset of chronic rejection [123].

Pneumocystis jirovecii is rare due to prophylaxis maintained with Septrin forte up to month 9. The incidence increases in patients with chronic rejection and long-term high immunosuppression. Mortality is considerable given its seriousness and diagnostic difficulties with specific treatment. Its diagnosis requires BAL positivity, and frequently the gravity of the patients prevents a bronchoscopy (particularly if the patient is not intubated) and much less a correct BAL, which also reduces its diagnostic utility.

A high-resolution CT scan and ventilation/perfusion gammagraphy may aid diagnosis. Treatment is with sulfamethoxazole/ trimethoprim or co-trimoxazole. Corticosteroids (methylprednisolone 40 mg/8 hours IV) should be added in the first days to reduce an inflammatory reaction causing the rupture of cysts, administer folic acid during treatment [124].

Tuberculosis is rare in lung transplant patients and requires confirmed positive culture (in addition, do BAS culture and BAL) to start treatment [125], given the interference of rifampicin with cyclosporine and tacrolimus (necessitates a large increase in dose to reach correct levels). Treatment with the three usual drugs (isoniazid + pyrazinamide + rifampicin) during first 2 months, continuing with 2 drugs (isoniazid + rifampicin) 6-9 months.

Chronic graft dysfunction

This represents the main cause preventing the long-term survival of a transplanted patient and affects 50% or more of patients who survive over 5 years.

This entity has traditionally been defined as bronchiolitis obliterans syndrome (BOS), and consists of the inflammation, destruction and fibrosis of small airways. So, the best diagnostic test is a compatible lung biopsy. As this is not always possible, a constant drop in forced expiratory volume in 1 second (FEV_1) less than or equal to 80% of baseline posttransplant FEV_1 is used as clinical marker [126]. Baseline FEV_1 is the

mean of the 2 highest FEV_1 values obtained with at least 3 weeks' difference without administration of bronchodilators.

There is a long list of worsening functional capacity causes during follow-up, so differential diagnosis is necessary with other non-BOS inflammatory processes (acute rejection, lymphocytic bronchiolitis, humoral rejection) inflammatory complications of graft, infections, chronic vascular alterations, hyperinflation of native lung, alteration of bronchial anastomosis, etc. [127].

Although there are immunological causes responsible for the onset of BOS (acute rejection, humoral rejection and lymphocytic bronchiolitis are the only non-triggering factors). This graft damage during primary dysfunction, gastroesophageal reflux, different infectious aetiologies, etc., have shown an important role in the pathogenesis of BOS [128]. Thus, tissue damage and inflammation due to non-immune factors might stimulate the recipient's alloimmune response, with OB (obliterative bronchiolitis) being the final result of the process.

Depending on the degree of FEV_1 deterioration, a BOS grade classification was established in 1993 [126]. It was subsequently revised in 2002, adding a drop in forced expiratory flow 25-75% (FEF 25-75%), as first functional alteration due to small airway affectation 2002 [129] (Table 1).

The 2002 classification added 0-p as potential or incipient BOS.

BOS is not the only condition within the concept of chronic lung allograft dysfunction (CLAD); there are also other patterns that include partial reversibility of airway obstruction, restrictive ventilation deterioration and pulmonary parenchymal alterations [130].

Reversible neutrophil graft dysfunction is characterized by presenting neutrophils in BAL with a neutrophil count over 15% and an improvement in FEV_1 after treatment with azithromycin [131].

Restrictive allograft syndrome (RAS) is another chronic dysfunction in which total lung capacity (TLC) declines over 10% from the baseline value. Imaging test findings show anatomical fibrosis predominant in the upper lobes. The prognosis is worse than for BOS [132].

With compatible symptoms we must conduct a complete study, including full respiratory function tests that include lung volume, a high-resolution CT scan (peripheral hypovascularization, air entrapment areas associated with small atelectasis and peripheral bronchiectasis), a simple radiology may be normal, and a bronchoscopy with transbronchial biopsy and BAL, which is indicated to rule out infection, although the diagnostic utility in BO is low due to patchy affectation.

Although the response to established dysfunction is poor, the aim is to achieve small improvements or stabilize lung capacity.

Treatment consists of increasing immunosuppression and preventing the development of infections. High-dose corticosteroids have shown side effects but no benefits, so they are not recommended [127].

Regarding patients whose immunosuppression is based on cyclosporine A, the treatment has demonstrated clinical stability [127,133]. However, replacement of mycophenolate mofetil by everolimus currently shows no benefits regarding the progression of BOS [134].

The use of azithromycin is beneficial for 35-40% patients, particularly those with neutrophilia in BAL [135]. Treatment consists of 250 mg/24 hours for 5 days and then 250 mg/48 hours indefinitely.

Patients with BOS and proven gastroesophageal reflux (oesophageal pH probe) should undergo anti-reflux surgery based on the patient's surgical risk [127].

In young patients (<55), with good general condition, who have no heart or kidney dysfunction and meet transplant criteria, the final treatment option for chronic rejection is a retransplant, performed preferably on ambulatory patients. Initial mortality is higher than the first transplant, however, for selected patients and in centres with experience, survival may be similar to the initial transplant [136].

Development of neoplasms

An increase in the number of lung transplants combined with better survival leads to a higher incidence of neoplasms. At 5 years this is 10-12% and at 10 years, 20-30%, according to ISHLT international registry data [4].

The most common neoplasms are skin and posttransplant lymphoproliferative disease, whose most serious version is lymphoma.

Skin neoplasms that receive appropriate treatment generally have a good prognosis.

Lymphoproliferative disorders are more frequent in lung transplant than in other solid organs, perhaps due to the higher level of immunosuppression. These disorders mainly present in the first year post-transplant and are more frequent in young recipients. Their connection with Epstein-Barr virus infection has been described, particularly in patients with negative pretransplant serology. They usually combine pulmonary lesions or nodes with disease at other levels, lymph gland, brain, etc.

Treatment consists of reducing immunosuppression levels as far as possible without risking lung rejection, combining cyclosporine or tacrolimus with everolimus due to their antiproliferative antitumoral effect. Treatment is added with rituximab, an anti-CD20 chimerical monoclonal antibody; and in lymphoma cases with bad response, chemotherapy specific to the lymphoma type will also be administered. Mortality is approximately 50% of cases.

Other tumour types are possible, considering recipient age, and carcinoma may appear in the native lung, prostate, digestive system, etc. Despite the close follow-up of lung transplant patients, diagnosis is usually made at an advanced stage and has a bad prognosis. Again, treatment involves a reduction of immunosuppression levels when possible, an association with everolimus and specific tumour treatment, as well as surgical and oncological solutions [138].

Finding pulmonary neoplasms in the lung to be explanted is rare (<1%), particularly in PF cases. After verifying the good healing of the bronchial suture, treat with everolimus and closely follow up the patient with a thoracic-abdominal CT every 6 months. Prognosis depends on tumour stage and recurrence is common.

Table 1. BOS grade classification

	Classification 1993	Classification 2002
0	FEV_1 ≥80% FEV_1b	FEV_1 >90% FEV_1b and FEF 25-75% >75%
0-p	Not included	FEV_1 81-90% FEV_1b and/or FEF 25-75% ≤75%
1	FEV_1 66-80% FEV_1b	FEV_1 66-80% FEV_1b
2	FEV_1 51-65% FEV_1b	FEV_1 51-65% FEV_1b
3	FEV_1 ≤50% FEV_1b	FEV_1 ≤50% FEV_1b

FEV_1b: Baseline FEV_1

3. IMMUNOSUPPRESSIVE THERAPY

As induction treatment, methylprednisolone bolus are used, associated or not with other agents like OKT3, anti-thymocyte globulin (ATG), alemtuzumab and basiliximab. As the incidence of infection is higher with OKT3, most centres use ATG, basiliximab or alemtuzumab in combination with corticosteroids [139]. These treatments provide greater immunosuppression during the period of greatest rejection risk, and when correct levels have not been obtained with other immunosuppressives in blood. This treatment regime is used in 50% of centres [140].

Maintenance treatment is based on steroids, calcineurin inhibitors (cyclosporine A or tacrolimus) and an antimetabolite (azathioprine, mycophenolate mofetil, sirolimus and everolimus).

Most centres use tacrolimus [141] as a calcineurin inhibitor agent, although differences regarding acute rejection are unproven, it seems to present a lower incidence in the long term than for BOS [142].

Although mycophenolate is the most widely used agent [141], it has not shown better results than azathioprine [143].

The use of sirolimus and everolimus is frequently motivated by kidney dysfunction due to calcineurin inhibitors [144], the onset of BOS [145] and malignancy. Precisely because of their antiproliferative and anti-fibroblast effect they are not used during the immediate posttransplant period since they hinder healing and favour the onset of dehiscence [146].

The side effects of immunosuppressive drugs are responsible for significant morbidity, so the purpose of follow-up is to detect and control this toxicity where possible [74] (Table 2).

Table 2. Side effects of Immunosuppressive drugs

Drugs	Side effect
Antimetabolite (azathioprine, mycophenolate mofetil)	Myelosuppression, intestinal intolerance, liver toxicity, infections, tumours
Calcineurin inhibitor (tacrolimus, cyclosporine)	Nephrotoxicity, hypertension, hyperuricemia, hyperlipidaemia, diabetes, hyperkalaemia, neurotoxicity, infections, tumours
mTOR inhibitors (sirolimus, everolimus)	Hyperlipidaemia, diabetes, pneumonitis, infections
Steroids	Hyperlipidaemia, diabetes, hypertension, hypocalcaemia, infections, cataracts, weight gain

4. FOLLOW-UP

The periodicity of check-ups is motivated by immunosuppression adjustment periods, particularly progressive corticosteroid reduction and the suspension of prophylaxis. The frequency should be higher if the patient's situation requires it or if specific adjustments are necessary. General recommendations are:

- Until month 6, every 4-6 weeks.
- From months 6 to 12 inclusive, every 8 weeks.
- Years 2and 3, every 3 months.
- From year 3, every 4-6 months.

Tests to be performed generally are:

- All check-ups: analysis with haemogram and complete biochemistry (including iron and magnesium), CMV PCR, immunosuppression plasma levels, spirometry.
- Chest X-ray in 2 projections, at an early stage, alternating every 2 appointments, every 3-6 months, and whenever indicated [74].
- Chest CT: the first month after surgery, whenever indicated by clinical findings or spirometry results [147].
- Creatinine clearance test and 24-hour urine proteinuria study advisable every year or when kidney failure is detected.
- After posttransplant control bronchoscopy performed on demand according to patient's clinical situation [148]:
    1. Suspected acute rejection with bad response to corticosteroid bolus treatment.
    2. Suspected complications with bronchial suture (particularly stenosis) via CT or X-ray.
    3. Suspected chronic rejection by spirometry, or symptoms to confirm it and rule out acute associated component and infections.
    4. Before moderate and serious infections or with bad response to antibiotic treatment.
    5. Diagnosis and control of fungal infections, mycobacteria infections, *Pneumocystis jirovecii* infection.
    6. To clean and aspirate purulent secretions in patients with aggressive germ infections, in particular *Pseudomonas* infections in CF.

CONCLUSIONS

» Treatment options depend on PGD grade and clinical situation of the patient, i.e., an increase in mechanical ventilation associated with negative balances and use of pulmonary vasodilators (prostaglandins and inhaled nitric oxide). Use of ECMO in patients with grade 3 primary failure is clearly established today.

» Infections represent 35% first year deaths and are the main cause of death during this period. The pathogenesis of chronic rejection likewise plays an important role, hence the importance of prophylaxis and early treatment. The most common presentation is pneumonia.

» Chronic graft dysfunction represents the main cause preventing the long-term survival of a transplanted patient, affecting 50% or more of patients who survive over 5 years. This entity is traditionally defined as bronchiolitis obliterans syndrome (BOS), consisting of inflammation, destruction and fibrosis of small airway causing an OB.

» Neoplasms are seen more frequently, driven by the increase in the number of lung transplants in addition to better survival. Their occurrence is 10-12% at 5 years and at 20-30% at 10 years.

» The frequency of check-ups is motivated by the periods of immunosuppression adjustment, particularly the progressive reduction of corticosteroids and the suspension of prophylaxis. The frequency of check-ups should be guided by patient situation and specific adjustments required.

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TOPIC 7 - Unit 1

General aspects of living donation

ORGAN TRANSPLANTATION

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INTRODUCTION

Objectives

The subject of this unit is living donation (LD):

- Despite its results, LD remains a controversial subject that generates medical and ethical debate. In this unit we discuss the most relevant medical, ethical and legal issues of living donation.
- First, we give a general overview of the history of living donation and the current state of the art
- Secondly, we discuss which conditions should be met in order to be a living donor, covering the most relevant medical and ethical issues on living donation.
- Finally, we present the most important international laws and regulations on living donation, in addition to some joint initiatives on the follow up of living donors in Europe.

1. LIVING DONATION AROUND THE WORLD

Since 1954, when the first LD kidney transplant between identical twins was performed in Boston [1], advances in the field of immunosuppressive therapies have contributed to the success of transplants from deceased donors which, in countries with a high rate of deceased donors, such as most European countries, meant a move away from the living donor alternative.

However, other advances, like the use of less invasive surgical techniques (laparoscopic nephrectomy) with a low rate of complications, and desensitization techniques for ABO-incompatible transplants, have led to an increase in living donation. Pre-emptive living donor kidney transplantation provides better outcomes, for both recipient and graft survival rates. The same may apply to other transplant organs from LD, which is the result of medical advances that allow less invasive surgical techniques for the retrieval and transplantation of organs, and the use of parts (segments) of organs, such as liver, lung, small intestine and pancreas [2-5].

Rates of living donation may vary between different countries depending on the level of development of deceased donation, as well as other cultural and social issues.

In Asia, the majority of organs used for liver transplant come from LD [6]. This could be a consequence of the low deceased donor rate, due to cultural and religious conflicts, and a lack of legislation on the diagnosis of brain death and professionalized transplant procurement management (TPM) teams.

Also, in countries where donation comes predominantly from deceased donors, LD donation has grown as a valid therapeutic option and as a new source of organs to increase the number available for transplant by complementing, not replacing, deceased-donor donation.

Living donation rates vary from country to country. For example, in 2012, LD donation rates for kidney transplants in Europe (per million population) ranged from 7.8 pmp in Spain to 29 pmp in the Netherlands. In the USA, the rate was 15 pmp, in Australia 10.4 pmp and Canada 12.3 pmp. Different figures are found in Asia and Latin America, where the deceased donor programmes are still not well developed. In Argentina, the living donation rate reached 7.1 pmp and in Mexico, 16.7 pmp [7].

Interesting data comes from Iran, where a kidney transplant programme was started in 1967; by 1999, the kidney waiting list was fully covered [8]. With a population of 76 million in 2012, the LD rate was 19.7 pmp [9].

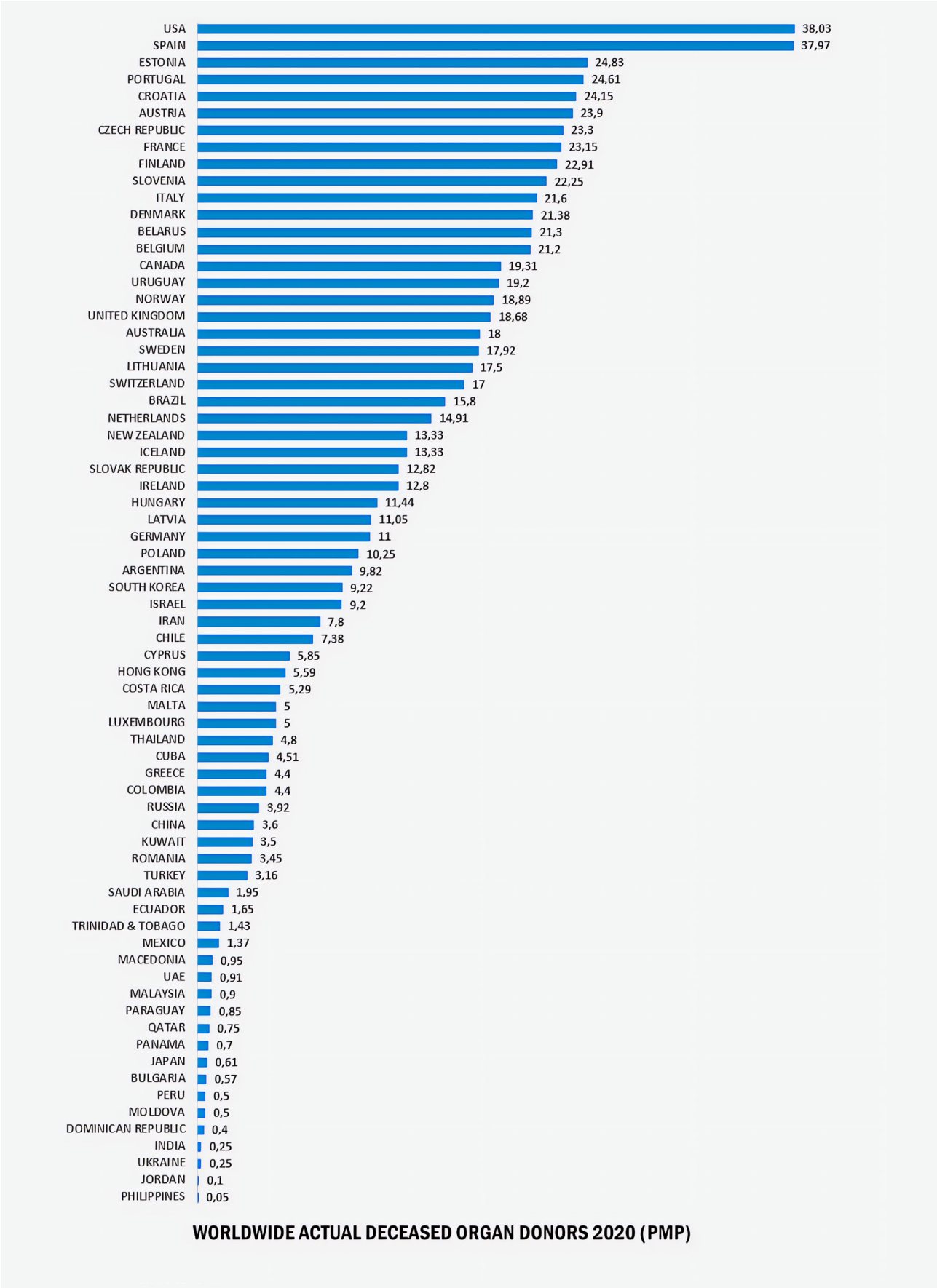

Figure 1. Worldwide DCD donors (pmp) 2013.

2. WHO CAN BE A LIVING DONOR: ETHICAL CONSIDERATIONS

Initially, living donation was restricted to genetically related persons, but advances in immunosuppressive therapies have allowed the potential donor pool to expand to people who are not genetically related.

However, this has caused doubts about the donor's motivation to donate. Several authors defend donors with a long-standing, stable emotional relationship with the recipient as there is an ethical motivation to want to help their loved one, whether there is a genetic relationship or not [10-12].

Altruistic donors, also called "good Samaritans," who wish to donate voluntarily to an unknown person on the waiting list have also generated great controversy. Some authors consider that this type of donor may suffer some kind of psychosocial disorder, be donors under duress, family pressure or donate for financial reasons. However, if none of the above factors is proven, there are no reasons to exclude good Samaritan donors [13,14].

Living donation is a process that brings out the best of humans and helps reduce mortality rates among waiting-list patients. However, the medical guidelines, legal conditions and practices that determine who can become a donor may vary between countries, in different cultural settings, and even in centres within the same country.

"The medical guidelines, legal conditions and practices that determine who can become a donor may vary between countries, in different cultural settings, and even in centres within the same country".

In general terms, the donor must comply with the following requirements: a mentally competent adult who is willing to donate free of coercion and is medically and psychosocially suitable. In addition, donors must be fully informed of the risks and benefits of donation for both the donor and recipient, and of the existing therapeutic alternatives for the recipient [15].

This section discusses the following ethical issues that arise in LD.

- Motivations for living donation
- Risk benefit assessment of living donation
- Informed consent

2.1 Motivations for living donation

The feelings and motivations experienced by a person who is planning to become an LD, and the way in which the decision-making process is conducted are subjects that have generated much interest. A number of authors have attempted to explain the motivations and processes. Lennerling et al. [18] divide the motives into seven categories:

1. **A desire to help:** a powerful motive, frequently considered as
2. **Something natural:** the donor simply wants to help a family member or close friend in need.
3. **Increased self-esteem:** doing something that is good makes them feel a better human being.
4. **Identification:** with the recipient's situation.
5. **Self-benefit:** from the relative's improved health. Donors they assume donation will increase joint quality of life in many ways.
6. **Logic:** it is a rational process to analyse risks and benefits. "If I can live with one kidney, why shouldn't I donate..."

7. **External pressure:** coercion by third parties.
8. **Feelings of moral obligation:** "Donation is something that you are expected to do..."

Of all the above, external pressure is the only unacceptable category. The motives are definitely based on subjective feelings. The donor's decision is mainly based on emotions, rather than on a risk-benefit analysis [17].

"External pressure is the only unacceptable reason for living donation."

2.2 Risk benefit assessment of living donation

In living donation, the key question has always been, "Is it justified to put the life of one person at risk to save or improve the life of another?" In the early years of transplantation, the answer was yes, due to the low surgical risk for living kidney donation, the strong wish to save the life of a loved one and the lack of another treatment alternative. However, since then, the situation has changed due to developments in deceased-donor transplantation, thanks to the advances in the field of immunosuppression, the availability of alternative treatments such as dialysis, and the possibility of living donation of portions of an organ, as in the case of the liver.

Table 1 summarizes the most relevant benefits and risks of living donation.

Table 1. Principal benefits and risks of living donation for donors

Benefits of living donation	Risks of living donation
Better graft quality: due to good health of the donor, avoiding any possible organ damage secondary to brain death or during extended cold-ischaemia time.	Short term: morbidity-mortality associated with the surgical process. This is lower in kidney transplantation, especially since the introduction of laparoscopic nephrectomy, and considerably higher in hepatectomy of the right lobe of the liver.
Possibility of choosing when transplant is performed, such as in cases of pre-emptive kidney transplantation. This helps avoid deterioration of recipient's health, increasing the possibility of a successful transplant.	
Increases the donor pool: better access to transplant for the recipient and reduced waiting times for other recipients on the waiting list; especially young kidney recipients, where the chances of obtaining an age-appropriate deceased donor are lower.	Long term: the rate of long-term complications in living kidney donors has been shown to be very low but no data exist for the living liver donors.
Reduction of healthcare costs for society: there is confirmed lower cost from the first year in favour of transplantation when compared to dialysis treatments.	Psychological: depending on many factors, such as family conflicts, success of the transplant and the progress of the recipient.
Psychological benefits for the donor: increased self-esteem.	

All these factors have generated debate and discussion. Living donation brings two basic ethical principles into conflict: "beneficence" and "do-no-harm."

» **Beneficence** implies doing good, and this principle overrides the **"do no harm"** principle if the probability of benefit fully outweighs the risk of the injury to be inflicted [18,19].

» **Distributive justice:** This principle could particularly affect the lack of supply of organs from deceased donors. It is important to consider that any unnecessary restriction on living donation would worsen the severe scarcity of organs, leading to negative consequences for all potential recipients [18,19].

2.3 Informed consent

Informed consent is an expression of an individual's autonomy. Autonomy is one of the basic principles of biomedical ethics, which means that people choose and act freely and rationally. Informed consent requires the following [11,20,21]:

» mental competence or capacity to understand and assimilate all of the information provided;

» possession of all relevant information;

» free and voluntary decision;

» consent and signing of the document.

"The importance of informed consent relies on providing all necessary information to the potential donor in order to ensure that he or she understands the process and will make a deliberate decision."

It also requires time to give the donor the chance to assimilate all the information and have all their doubts clarified.

Potential donors must be informed about:

» the nature of the screening and evaluation process;

» the surgical procedure and its associated mortality and morbidity risks;

» the rehabilitation phase, with its social, emotional and financial consequences;

» long-term consequences of living donation.

The information should be given in both oral and written form, and it is often necessary to have more than one meeting with the donor to clarify different issues and questions. Another advantage of multiple consultations is that it gives the potential donors the possibility to evaluate the process thoroughly and reach a fully considered, informed decision. In this manner, it can be ensured that the motives for donation are truly altruistic, and that the written consent to living donation is based on a full comprehension of the donation process. Some countries have recommended that potential donors should be provided with independent counsellors to avoid any form of coercion of the donor. An assessment of the donors and the donor-recipient relationship by in-hospital or external ethics committees are usually required by the specific transplant laws.

A potential donor should not be burdened with financial or social difficulties during the assessment or donation process. Regulations on how to achieve this vary from country to country. In some parts of the world, certain forms of incentives for the donor are discussed. There is, however, a broad agreement within the transplant community that sale and purchase of human organs should be illegal and banned, as it is in most countries [22]. Further discussion of these aspects of LD is beyond the scope of this text. Once it is clear that one or more potential donors are motivated and that no obvious contraindications exist, the screening process goes ahead to ensure compatibility. Medical assessment is the final part of the selection process.

3. GENERAL CRITERIA FOR ACCEPTANCE OF A LIVING DONOR

Donor protection should always be guaranteed during the selection and assessment of a living donor [23]. The key factor for a successful living-donor programme is careful attention to every detail and the application of strict routines in the selection of donors to guarantee donor safety in the short and long term, and maximum success for the recipient [24].

Before donation

The living donor evaluation process follows a different schedule based on each particular case and on each centre's facilities. For every case, the process is divided into two phases.

- **The first phase** consists of an initial screening (using non-invasive, low-cost tests) that allows contraindications for donation to be ruled out (in both donor and recipient).
- **In a second phase**, the assessment of the donor varies according to donor characteristics (clinical and psychosocial) and type of organ.

The donor should, in principle, be free from any mental or physical illness, but certain deviations can be accepted without increasing risk for the donor.

Initial screening

- To quickly identify obvious contraindications
- To identify lack of motivation
- To identify obvious psychiatric disorder
- To identify any medical contraindication (i.e., hypertension, heart disease, malignant disease, diabetes mellitus)
- To ensure compatibility
- ABO and HLA typing

Clinical examination with emphasis on

- Coronary heart disease and cardiovascular risk factors
- Blood pressure (BP) below 140/90
- Body mass index (BMI) below 30
- Malignant disease with particular focus on breast, prostate and large bowel
- Any malignant disease other than *in situ* carcinoma of the skin should be avoided
- History of thromboembolism or bleeding disorder

Pulmonary function tests in patients at risk

- Vital capacity
- Forced expiratory volume in one second (FEV1) and/or peak expiratory flow (PEF)

Heart function tests

An ECG is performed for all subjects. Exercise ECG for all donors >40 years, and nucleotide perfusion imaging or stress echocardiography whenever any increased cardiovascular risk is perceived. A 24-hour blood pressure examination should be performed on all subjects in whom uncertainties concerning the BP are raised.

Imaging

- Chest X-rays
- Abdominal ultrasound
- Computerized tomography (CT) and magnetic resonance imaging (MRI) of the abdomen

Lab tests

- ABO and tissue typing (duplicate tests)
- Viral serology for HIV, HBV, HCV, CMV, EBV, syphilis and *Toxoplasma*
- General lab values (haematology, liver function, kidney function)

Other health professionals who should evaluate the donor

- Physician, independent of the team carrying out the transplant
- Anaesthetist
- Social worker
- Psychologist or psychiatrist if indicated
- For abnormal findings, all relevant medical sub-specialties should be consulted

After donation

"Every living donor should be offered a structured follow-up programme ensuring that any side effects or complications of the donation are detected as early as possible and treated promptly"

Another important impact of the follow-up programme is that this is the only way to assess the true performance of the medical treatment the donors are given, and possible negative effects caused by the procedure. Regular medical consultations are an additional benefit of the donation. Donors should be seen at regular intervals (for example at 1, 3 and 12 months after the operation and then yearly).

4. LEGAL REGULATIONS & REGISTRIES

Living donors need to be protected, and this is the aim of major organizations that are working to create regulatory guidelines which ensure the safety and security of LD.

Likewise, all transplant programmes must make it a priority to ensure the existence of a living donor registry and provide comprehensive protection. A registry represents the transparency of living donation programmes and the traceability of the organs.

This section provides a brief summary of the most relevant regulations and registries put in place in Europe:

» **Legal regulations**

» **Joint initiatives**

4.1 Legal regulations

The World Health Organisation (WHO) [9] issued its Guiding Principles on Human Cell, Tissue and Organ Transplantation, the Amsterdam Forum issued an international Consensus Statement on live kidney donation, and the Vancouver Forum did so for living donation of other organs.

The European Council has also created a series of recommendations on living donation, contained in an Additional Protocol of The Convention on Human Rights and Biomedicine on Transplantation of Organs and Tissues of Human Origin, drawn up during the Human Rights and Biomedical Convention, and formally approved by the Committee of Ministers in Strasbourg (24 January 2002), in addition to other considerations for the living donor published in the "Guide to Safety and Quality Assurance for Organs, Tissues and Cells" [25].

In Appendix 5 of the Protocol, Chapter III "Organ and tissue removal from living persons", articles 9 to 15 make the following recommendations:

a. General rule: Removal of organs or tissue from a living person may be carried out solely for the therapeutic benefit of the recipient and where there is no suitable organ or tissue available from a deceased person and no other alternative therapeutic method of comparable effectiveness.

b. Potential organ donors: Organ removal from a living donor may be carried out for the benefit of a recipient with whom the donor has a close personal relationship as defined by law, or, in the absence of such relationship, only under the conditions defined by law and with the approval of an appropriate independent body.

c. Evaluation of risks for the donor: Before organ or tissue removal, appropriate medical investigations and interventions shall be carried out to evaluate and reduce physical and psychological risks for the health of the donor. The removal may not be carried out if there is a serious risk to the life or health of the donor.

d. Information for the donor: The donor and, where appropriate, the person or body providing authorization (Article 14, paragraph 2), shall beforehand be given appropriate information as to the purpose and nature of the removal as well as on its consequences and risks. They shall also be informed of the rights and the safeguards prescribed by law for the protection of the donor. In particular, they shall be informed of the right to have access to independent advice about such risks by a health professional having appropriate experience and who is not involved in the organ or tissue removal or subsequent transplantation procedures.

e. Consent of the living donor: Subject to Articles 14 and 15, an organ or tissue may be removed from a living donor only after the person concerned has given free, informed and specific consent to it either in written form or before an official body. The person concerned may freely withdraw consent at any time.

Protection of persons not able to consent to organ or tissue removal:

1. No organ or tissue removal may be carried out on a person who does not have the capacity to consent under Article 13.
2. Exceptionally, and under the protective conditions prescribed by law, the removal of regenerative tissue from a person who does not have the capacity to consent may be authorized provided the following conditions are met:
   i. there is no compatible donor available who has the capacity to consent;
   ii. the recipient is a sibling of the donor;
   iii. the donation has the potential to be lifesaving for the recipient;
   iv. the authorisation of his or her representative or an authority or a person or body provided for by law has been given specifically and in writing and with the approval of the competent body;
   v. the potential donor concerned does not object.

Directive 2010/53/EU of the European Parliament:

Directive 2010/53/EU of the European Parliament and of the Council on standards of quality and safety of human organs intended for transplantation [26] adopted on 7th July 2010 and to be transposed by Member States until 27th August 2012.

The Directive establishes the basic requirements for the protection of the donor, including data protection and confidentiality (Article 16), the need for consent (Article 14) and the voluntary and unpaid nature of the donation (Article 13).

In addition, the Directive contains a number of measures aimed at protecting living donors. These include a correct assessment of the donor's health and comprehensive information about the risks prior to the donation (Article 7), and the development of registers for living donors to follow up their health status (Article 15).

Article 15: Quality and safety aspects of living donation: Member States shall:

1. Ensure the *"highest possible protection of living donors."*
2. Ensure that *"living donors are selected on the basis of their health and medical history, by suitably qualified or trained and competent professionals. Such assessments may provide for the exclusion of persons whose donation could present unacceptable health risks."*
3. Ensure that *"a register or record of the living donors is kept, in accordance with Union and national provisions on the protection of the personal data and statistical confidentiality."*
4. *"Shall endeavour to carry out the follow-up of living donors and shall have a system in place in accordance with national provisions, in order to identify, report and manage any event potentially relating to the quality and safety of the donated organs, and hence of the safety of the recipient, as well as any serious adverse reaction in the living donor that may result from the donation."*

4.2 Joint initiatives

Living donor registries should be in place and used in order to be able to audit the LD programme easily at regular intervals. Besides hospital, local or national registries, there are some European initiatives on the registry and follow-up of living donors.

European Living Donation and Public Health (EULID, 2007-2009) promoted and coordinated by Hospital Clinic de Barcelona with the collaboration of 10 European countries. The EULID project aims to analyse the situation in European countries regarding legal, ethical, protection and registration aspects relating to living donors and living donation, in addition to making consensual recommendations on these issues and creating tools for use in all living donation programmes to guarantee the health and safety of living donors. Results of this project include an on-line database to register living donors, an informative leaflet for the public about living donation and a satisfaction survey for the donation process [27,28].

European Living Donor Psychosocial Follow-up (ELIPSY, 2009-2012) [28] promoted and coordinated by the Hospital Clinic de Barcelona with the collaboration of six European partners. The aim of the ELIPSY project is to contribute towards guaranteeing high-quality living organ donation programmes by creating a follow-up model for the psychosocial well-being and quality of life of living donors. The impact of the recipient's outcome on the donor and the donor's perception of the process will also be evaluated in the follow-up model. The ELIPSY project contributes to harmonisation of living donor psychosocial follow-up practices, promoting high-quality living donation programmes.

The main conclusions of the ELIPSY project were:

- The survey about current psychosocial assessment/follow-up practices conducted in 52 centres from 10 countries showed no consensus among them.
- The methodology applied to evaluate short- and long-term psychosocial follow-up of living donors showed no significant differences in the psychosocial outcome of living donors compared to the healthy general population.

CONCLUSIONS

» Living donation should complement deceased donation; it should never replace it.

» The outcome of LD transplants is better than the outcome of deceased donor transplants. Donor morbidity and mortality is low.

» Living donor transplant programmes must scrupulously comply with ethical principles and the legislation in force in each country, avoiding inappropriate practices, commercialization and trafficking of organs.

» The integral protection and registry of the living donor must be a priority in all transplant programmes.

» A registry represents the transparency of living donation programmes and the traceability of the organs.

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TOPIC 7 - Unit 2

Living liver and kidney donation

ORGAN TRANSPLANTATION

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INTRODUCTION

Although there are other organs or segments of organs that can be transplanted from living donors such as lung, small intestine and pancreas, kidney and liver continue to be the most frequently transplanted organs.

Objectives

In this unit we discuss specific issues related to the living donation of kidney and liver such as:

- The advantage that transplantation of kidney and liver from living donors may represent as an alternative to deceased donation.
- The specific clinical and anatomical requirements to achieve successful living donation and transplantation of these two organs.
- The technical surgical challenge that retrieval of these organs from living donors may represent.
- The immediate (post-surgical) and long-term consequences that living kidney and living liver donation may pose to the donors.

1. LIVING KIDNEY DONATION

In 1954, Murray and colleagues performed the first successful living donor (LD) kidney transplant in Boston on identical twin brothers [1] and by the late 1960s, LD transplantation was introduced as a standard part of renal replacement therapy in Europe and North America. In some countries such as Norway or the United States, LD kidney transplantation constitutes up to half of the total number of renal transplants. Today, the concept of using live donors has gained widespread acceptance around the world as the treatment of choice for patients with end stage renal disease (ESRD).

1.1 Advantages of living donor renal transplantation

Renal transplantation is a life-saving procedure [2] and it is well documented that living-donor kidney transplantation (LDKT) offers significantly better graft and patient survival compared with deceased-donor (DD) kidneys [3,4].

Living-donor kidney transplantation (LDKT) offers significantly better graft and patient survival compared with deceased-donor (DD) kidneys.

Morbidity and mortality rates for patients on the waiting list are clearly related to the time on dialysis [2] and it is recognized that ESRD increases cardiovascular mortality by a factor of approximately ten.

One important aspect of LDKT is that it allows for planned, elective procedures, thus making the waiting time on dialysis shorter and the concept of pre-emptive transplantation possible and feasible in practical terms.

Living-donor grafts appear to have better functional outcomes (Figure 1) and even better graft survival rates in 2 haplotype mismatched LD transplantations compared with zero-mismatched DD grafts [3,4].

The improved survival is most likely related to several different factors, such as high-quality donor selection, optimal timing of the transplant, short cold-ischaemia time and avoidance of the pathophysiological alterations induced by brain death. Living-donor renal transplantation is especially well suited to paediatric recipients, as it minimises waiting time and the need for dialysis. From a public health perspective, the use of live kidney donors is the only way to provide functioning renal grafts within a reasonable period of time to a large proportion of candidates who are waiting.

Comparing the incidence of renal failure and transplantation rates internationally, it is evident that countries with well-developed LDKT programmes have the highest transplantation rates and the shortest waiting lists. As a result, a larger proportion of patients treated for ESRD have a functioning graft instead of being dialysis dependent. At the same time, this also has a significant economic impact, because it significantly reduces the need for costly dialysis treatment.

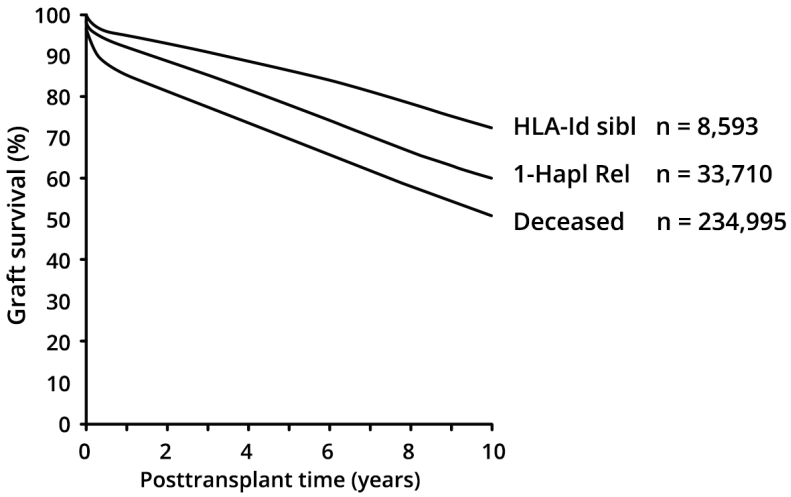

Figure 1. Graft survival after first renal transplant according to donor source.

HLA-Id: HLA- identical; 1-Hapl Rel: Haploidentical related donor. (www.ctstransplant.org)

1.2 Who can be a living kidney donor

The ideal living donor is a healthy adult member of the patient's immediate family and the majority of LDKT are still from related donors. However, the use of genetically unrelated but emotionally linked donors has gained widespread acceptance worldwide [3,4] and various guidelines have been introduced [5,6].

Another alternative in living kidney donation is cross-over donation, [7] also called paired kidney exchange (Figure 2). In 1986, Rapaport et al. [8] proposed the idea of paired kidney exchanges in an attempt to increase the availability of organs for transplantation.

Successful LD swap and swap-around exchange programmes require a large pool of donor-recipient pairs who are incompatible and all types of LD –relatives, spouses, close friends and voluntary donors– are potentially available.

There is also the exchange of living kidney donors between ABO incompatible donor-recipient pairs. This procedure started in 1991 in South Korea, since then is considered ethically acceptable, and has become commonly used in other countries like the USA, Netherlands and United Kingdom, in national or regional programmes. The donor-recipient pair must be completely informed about the characteristics of the other pair and the surgical procedure must be performed simultaneously.

Another proposal is list-paired exchange, in which a living donor who is incompatible with his/her recipient provides a graft to a patient on the deceased-donor waiting list in exchange for giving transplant priority to the recipient who provided the living donor.

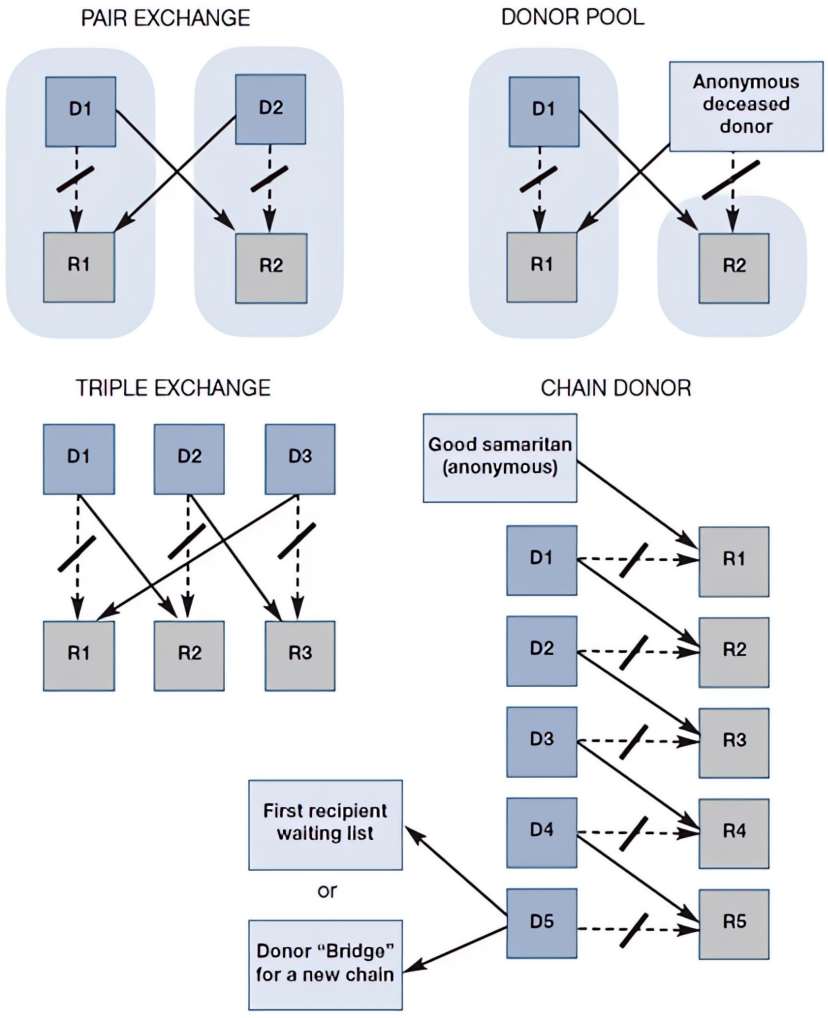

Figure 2. Kidney exchange: different options (D: donor; R: recipient; continuous line: compatible match - transplant; discontinuous line: no compatible match).

1.3 Specific clinical evaluation of living kidney donors

Besides the general clinical evaluation that every potential living donor should undergo before donation is performed (see Unit 1), there are specific organ-related issues that must be assessed in all living kidney donors, such as:

A thorough **renal function evaluation**:

- Assessment of glomerular filtration rate (GFR) should not only be conducted by formulas but should include creatinine clearance (repeated determinations) and/or isotopic determinations of GFR. Measured GFR should be over 70 ml/min.
- Radionuclide imaging might be indicated in cases where significant differences between the right and left side are suspected (>60/40). In this case, the nuclear imaging can be used to evaluate whether the poorer functioning kidney provides acceptable renal function for the recipient.

The use of imaging can assist us in determination of the presence of structural abnormalities and renal function.

- CT-angiography with arterial, parenchymal and excretory phase.
- Ultrasound of any undetermined renal cyst.
- Magnetic resonance imaging (MRI) can be used, but has lower sensitivity than CT.

Lab tests, such as urine examination should be double checked for:

- dipstick: albumin, blood, glucose;
- microbiological;
- microscopy.

Several clinical findings in the evaluation of potential living kidney donors may advise decisions on an individual basis:

- Abnormal urine findings (microscopic haematuria might be accepted after full workup).
- Marginal renal function in the elderly donor (GFR below 70 ml/min/1.73 m^2).
- Discrete unilateral renovascular abnormalities (must be judged on an individual basis, and the affected kidney must be used).
- Borderline blood pressure.
- Overweight (BMI >30).
- Patients with some hereditary nephropathies such as autosomal dominant polycystic kidney disease (ADPKD), Fabry disease and Alport syndrome may be candidates for kidney transplantation from kidney donors. Although renal transplant from a related living donor is not contraindicated in most nephropathies that have an autosomal recessive mode of inheritance, caution should be observed, and the disease must be excluded in the donor by imaging and/or genetic testing. Potential living related donors for patients with Alport syndrome should be evaluated carefully for the presence of microhaematuria and microalbuminuria and should be informed about the possible long-term increased risk of renal dysfunction associated with donation [9].

1.4 Living donor nephrectomy

Living donor nephrectomy represents a major surgical procedure in a healthy individual who will receive no direct benefit from the operation itself. It is therefore of utmost importance that the preoperative medical records are checked and re-evaluated by the surgeon responsible, and that the surgical team has the necessary skill and experience to perform the donor operation with the highest quality and the lowest possible rate of complications.

In some donors, abnormalities might be found that can be adequately addressed by suitable prophylactic measures. Which side to choose is determined by surgical anatomy, any split function differences and other factors relating to the donor, such as scars and perceived difficulties in positioning on a particular side.

The general principle is that the donor should always be left with his/her best kidney if there are side differences. When both kidneys are evaluated as equal, the kidney chosen should impose the lowest surgical risk on the recipient (i.e., avoiding multiple arteries).

Various techniques are available for donor nephrectomy. Open and endoscopic approaches are practiced and the decision about the technique largely depends on the surgical team and previous experience. Open donor nephrectomy has proven to be safe over the years. Since 1995, laparoscopic and retroperitoneoscopic donor nephrectomy have gained increasing popularity and are now standard in most centres. A few centres have gone one step further and offer transvaginal donor nephrectomy in selected cases [10]. These methods offer the donors faster recovery, less need for analgesia and cosmetic benefits without jeopardizing the donor or the graft [11-13]. It is, however, clear that there is a distinct learning curve for most surgeons in mastering laparoscopic operations, and endoscopic procedures are associated with some complications not seen in open surgery [14]. The choice of method must therefore be based on the skill of the surgical team, as well as anatomical and other donor-related factors.

1.5 Immediate and long-term consequences of living kidney donation

The risk of mortality with living donor nephrectomy is very low and estimated to be in the region of 0.03% [15].

Major surgical complications, such as significant bleeding, pulmonary embolism and deep infection are rare. The overall surgical complication rate is approximately 5-10% and the majority of complications are mild, not posing any risk of long-term morbidity [16,17].

Properly selected donors should not experience any increased risk of morbidity following donation. Unilateral nephrectomy in a healthy person (i.e., without hypertension, obesity or diabetes) is not associated with any increased risk of kidney disease in the long term.

Several studies have thoroughly investigated the long-term effects of kidney donation [18-21]. Such studies show that donors have a lower incidence of medical disability and sick leave, as well as a higher life expectancy than age-matched controls.

The incidence of hypertension is similar to or slightly higher in comparison with the general population and presents more often in older donors. Therefore, close monitoring is necessary to detect hypertension early and introduce appropriate treatment at the earliest date in order to prevent complications.

In older-aged donors or those who have a glomerular filtration rate in the lower normal range, a slight elevation of creatinine might be observed after the donation. It is possible that donation poses a particular increase in risk in older subjects [22]. In a limited number of cases, donors have presented ESRD; however, a number of studies report that the incidence is significantly lower than in the general population [18].

Nevertheless, the majority of studies on long-term risk have limitations since the follow-up periods are in general too short to evaluate lifetime risks. Furthermore, it might be questioned whether the control groups used are truly relevant, since they inherently include individuals that would not be eligible for kidney donation. A recent study from Norway with a very long follow-up period compared donors against

a cohort from a large observational population study whose subjects would be eligible as donors. The results showed a greatly increased lifetime risk of ESRD and an absolute increase in cardiovascular death of 2% over a 24.9 year follow-up period. The increased risk of ESRD might be related to hereditary factors since the majority of donors are genetically related. The risk of mortality is very moderate and occurs late in life, illustrated by the fact that the survival curves only began to separate beyond 10 years of follow up. These results do not justify modifications in current guidelines and should be evaluated by future studies; they further underscore the importance of regular donor follow-up and well-functioning donor registries [23].

2. LIVER DONATION

Living-donor liver transplantation (LDLT) was first contemplated to provide a solution for the lack of appropriate donors for children, whose waiting-list mortality rate was 30-40% [24-26].

The first successful transplant of this kind was performed in Australia, [27] and the first pilot experience was carried out by Broelsch in Chicago [28]; however, liver transplantation in children from living donors was largely developed in Japan since, due to the country's particular cultural beliefs, brain death is not accepted as confirmation of a person's death [29]. The results confirm the efficacy of this alternative, which gives good survival rates and has eliminated waiting list mortality.

Until 1993, all living-donor liver transplants were performed with the left liver lobe or segments 2 and 3 of the left lobe. This technique was also used for adult recipients in the United States but was abandoned because the liver mass in the left lobe was insufficient to cover these patients' needs. The right lobe of the liver, which represents around 60% of its total mass, solved this problem.

The first right-lobe liver transplant from a living donor took place in Japan in 1993, [30] with the first in the United States in 1997 [31]. If the initial liver mass is sufficient, the liver's enormous regenerative capacity determines rapid growth in both the donor and the recipient. The initial success of this technique, combined with the lack of deceased donors, has led to an increasing interest worldwide in living-donor liver transplantation in adults. More recently, thanks to advances in knowledge about the so-called "small-for-size" syndrome, LDLT using left liver as a graft is gaining increasing importance, both in Eastern and Western countries.

2.1 Advantages of living-donor liver transplantation

Liver transplantation is the only valid therapy for patients with end-stage liver disease [32]. Thanks to improvements in surgical techniques and advances in both the post-operative management of these patients and immunosuppressive therapies, survival rates of over 82% are currently obtained one year after transplantation [33]. As a result, there has been a significant widespread increase in the demand for liver transplants worldwide, essentially due to the incidence of chronic liver disease from hepatitis C virus and hepatocellular carcinoma, which is an indication for transplantation in selected patients.

In general, patients considered as candidates for living-donor liver transplantation must previously have met the requirements for inclusion on the transplant waiting list. Although this policy is controversial, LDLT provides the possibility of increasing the classic indications for liver transplantation, as in the case of older-age recipients or hepatocellular carcinoma, beyond the Milan criteria [34]. There are other diseases with poor outcomes after liver transplant, such as cholangiocarcinoma, [35] whose indication is only contemplated within the framework of controlled studies [36].

Nowadays, most waiting lists for liver transplantation are sorted using the MELD (Model for End-Stage Liver Disease) score, an objective system based on the calculation of three analytical parameters: serum bilirubin, INR (international normalised ratio) and serum creatinine [37]. This distribution system was introduced in the United States in February 2002, with the objective of reducing waiting list mortality in order to give priority to patients whose conditions were worse due to their liver disease, regardless of how long they had been on the waiting list.

According to this score, waiting list patients with intermediate MELD scores are the best candidates for LDLT, as they are less likely to receive a transplant from a deceased donor unless their clinical status worsens. This is an additional benefit in organ distribution, as it has been shown that the outcome of LDLT is worse in patients with higher MELD scores [38] and conversely, no clear benefit has been shown from transplantation in patients with MELD scores under 15 [39].

Once a patient is on the waiting list, they can be offered the possibility of LDLT in centres where the procedure is performed. To determine which recipients would most benefit from these procedures, besides the MELD score, consideration is also given to the reduction in waiting list time and, in cases of hepatocellular carcinoma, the possibility of scheduling the procedure before the disease progresses. Some additional advantages are the possibility of effectively preparing the patients for the procedure and of scheduling the best time to perform the transplant (e.g., HCV patients, who are administered antiviral treatment beforehand).

Furthermore, in the case of LDLT, the cold ischaemia time of the graft is generally less than 60 minutes, far less than with grafts from deceased donors, which reduces the possibility of graft dysfunction. This is also reinforced by the fact that the physiological changes that brain death determines, which are potentially detrimental and influence graft quality, are absent in grafts from living donors [40].

According to UNOS [41], to date there have been 4,909 LDLTs in adult recipients in the United States. The probability of graft survival (82.5 after one year, 72.2 after 3 years and 65.9 after 5 years) and patient survival (90.1 after one year, 82.5 after 3 years and 77.7 after 5 years) is similar to that currently obtained with grafts from deceased donors. Analysis of the experience in Europe up to 2011 reveals that 4,809 LDLTs were performed (ELTR information) [42], with an overall graft survival of 80%, 74%, and 69% at 1, 3 and 5 years, respectively.

2.2 Specific clinical evaluation of living liver donors

Assessment of possible donors begins when the transplant recipient and their family voluntarily request information about it after information on the process is offered. The minimum requirements for acceptance as a donor may vary from country to country or even between different hospitals. In general, acceptance criteria include age between 18 and 55, having a blood group identical to or compatible with the recipient's, and an apparently normal state of health with no associated diseases. However, applicability of the procedure is low, with less than one third of recipients having potential donors, and a rate between 14-25% who finally undergo LDLT [43-45].

The assessment process is not conducted by the transplant patient's own doctors, but by an independent team, which includes hepatologists, surgeons and psychologists.

One of the most important factors when determining donor suitability is the estimated liver volume, because if this is insufficient, it could have disastrous consequences for the recipient. Insufficient graft volume could lead to initial malfunction and loss of the graft, with the appearance of what is known as the "small-for-size" syndrome [46-50]. This syndrome is characterized by sustained cholestasis, abundant ascites and coagulopathy. The development of extrahepatic complications and sepsis can lead to the death of the patient.

Through the use of computer programmes, both computerized axial tomography and magnetic resonance imaging are capable of calculating the volume of all or part of the liver with a high level of reliability [51,52]. Their utility is evident, since they calculate the total liver volume of the potential donor and the re-

sidual amount of liver parenchyma after resection of the right lobe, generally used for an adult recipient.

The acceptable liver volume for transplant to guarantee adequate postoperative function is considered to be 0.8-1% of the recipient's weight [47,48,53-55]. Due to its larger volume, it is therefore necessary to use the right lobe for transplant into adult recipients.

Besides the size of the graft, another consideration is the severity of the recipient's disease, which also influences postoperative graft function and survival [55]. Patients with worse clinical conditions need larger grafts.

It is very important to obtain knowledge about the hepatic vascular and biliary anatomy before obtaining the graft in order to guarantee the success and safety of the surgery for both donor and recipient. The introduction of helical axial tomography and new MRI models have provided the possibility of minimally aggressive, detailed vascular and biliary studies of the liver [44,56]. The two tests are equally effective for evaluating the vascular distribution of the liver, but MRI is also capable of effectively evaluating the liver's biliary anatomy, so it is currently the gold standard in assessment of potential donors [53].

The division of the portal vein into its right and left branches presents variations in approximately 20% of all donors. Although the existence of a three-way division is not a contraindication, it must be taken into account when it comes to vein resection (Figure 3). The need for several portal anastomoses, with or without the use of grafts, increases the risk of postoperative thrombosis.

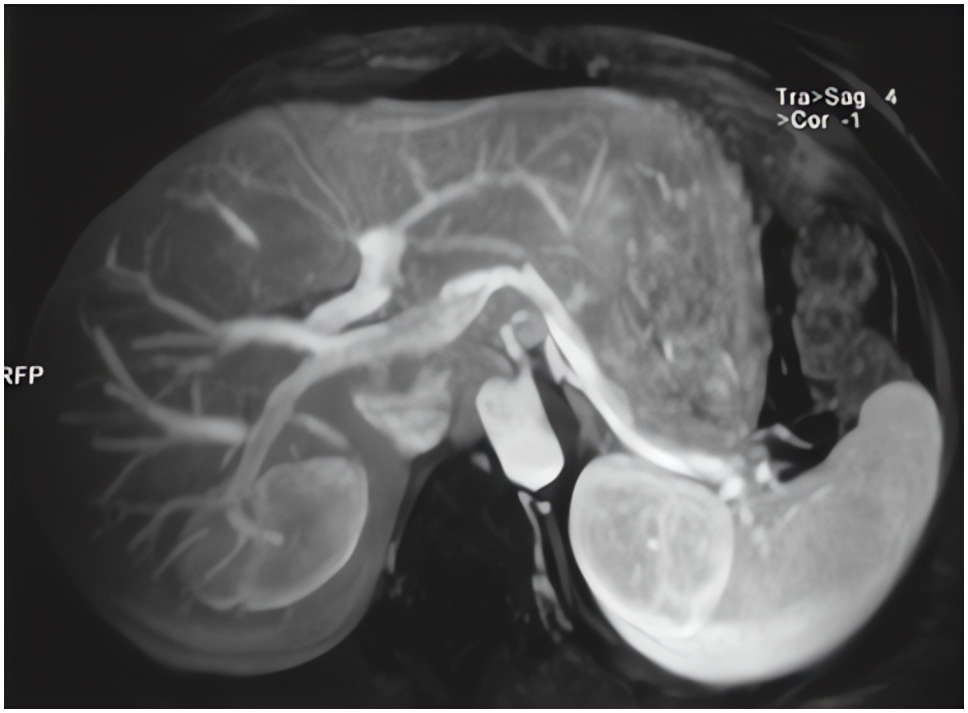

Figure 3. Magnetic resonance image of a donor, showing the existence of three-way portal branching. The anterior right portal branch originates from the left portal vein.

A complex arterial anatomy in the right lobe, such as multiple arteries, may be a reason for rejecting a donor, as there is a high risk of arterial thrombosis of the graft. If necessary, the hepatic vascular tree can be studied by angiography [57].

The distribution of veins in the liver can also present variations. If the lumen of these veins is larger than 5 mm, they must be anastomosed to the vena cava, either directly or using vascular grafts, to prevent them from compromising the graft's vascular drainage. Insufficient venous drainage and subsequent vascular graft congestion may lead to graft malfunction [58].

The bile duct is the structure with the largest number of anatomical variations, although this is not usually a contraindication for donation. However, reconstruction of the graft's biliary drainage system often gives rise to complications, although in most cases this does not compromise its viability [59]. A non-invasive test found to be effective for preoperative evaluation of biliary anatomy is an MRI-cholangiography [52,60].

2.3 Living donor hepatectomy

Right hemiliver donation

The surgical procedure for the donor consists of a right hepatectomy (segments 5, 6, 7 and 8) and it is advisable for the operation to be performed by two surgeons with considerable experience in liver surgery [61]. A J-shaped or right subcostal incision is made. Once the laparotomy has been performed, a complete and thorough examination is made of the abdominal cavity and the liver is mobilized by resecting its ligaments. Before starting resection of the hepatic parenchyma, the right portal artery and vein are temporarily clamped to delimit the parenchymal dividing line. An ultrasound scan is performed to visualize the middle hepatic vein and define the resection line, to the right of this vein, which remains in the left lobe of the liver. Resection and cauterization of the liver parenchyma is then performed, and intraparenchymal vessels larger than 3 mm are either tied or sutured. The right lobe of the liver is now completely separated, with its vascular structures remaining intact until the last minute when the graft is removed (Figure 4). The presence of accessory right hepatic drainage veins in the middle hepatic vein may lead to certain amount of venous congestion when they are tied. This reduces functional volume, so reconstruction must be considered according to the volume of the graft and the anatomy of the venous system.

Before removing the graft, the vascular structures are dissected and cut, starting with the right hepatic artery, always taking care not to compromise the contralateral structures. The vascular and biliary structures remaining in the donor undergo haemostatic suturing, and a final cholangiogram is advisable to detect possible leaks in the liver surface and the correct morphology of the remaining bile duct. After ensuring adequate haemostasis, the correct position of the left lobe of the liver is verified in order to guarantee correct portal patency.

After the graft is removed, it is perfused with a cold preservation solution through the portal vein and hepatic artery and stored at 4ºC until it is implanted. It is important to assess the anatomical structures and the need for repair. In cases of multiple right bile ducts, it is usual to perform ductoplasty.

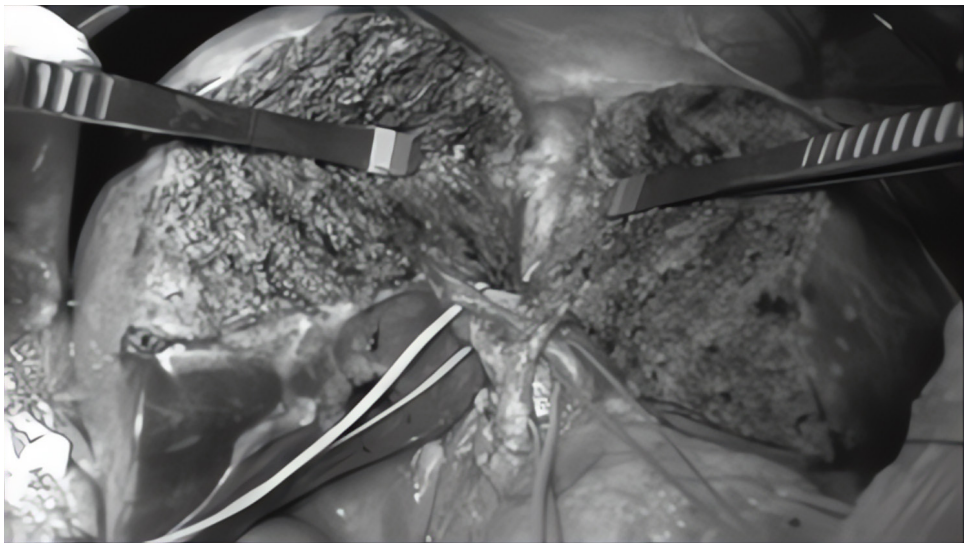

Figure 4. Picture of the end of liver resection. The complete separation of the right and left hepatic lobes can be seen, with the vascular structures remaining intact.

Left hemiliver donation

Although still not the gold standard in Western countries, there is a growing trend to use the donor's left liver as a graft, since this involves less risk for the donor, as well as being a slightly less demanding procedure.

The surgical procedure for harvesting the left hemiliver as a graft for transplantation consists of a standard left hepatectomy (segments 2, 3 and 4). The surgical steps of the procedure are similar to those used in right donation. First, the vascular and biliary anatomy is evaluated intraoperatively and compared to the preoperative findings. Then, liver transection is performed leaving the middle hepatic vein on the donor side. The process of cooling and perfusing the graft is identical to that described above for the right graft.

2.4 Immediate and long-term consequences of living-donor liver donation

The surgical procedure for right-lobe liver donation is not free of risk. The actual incidence of complications, however, is difficult to define due to a lack of uniformity in data collection. The absence of standardization in donor assessment and surgical procedure, as well as variations in the expertise and technical skills of different groups, make it difficult to evaluate the risks for donors. In 2006, seven patients were reported as having died from causes directly related to hepatectomy in the United States and Europe, representing a mortality rate of 0.15% [62]. There were another two reported cases of donors who committed suicide 22 and 23 months after donation. The psychological tests performed on these two cases prior to donation were normal, so it is difficult to determine whether or not their deaths were related to the donation process. With the inclusion of these two cases, the mortality rate rises to 0.2% [62].

The morbidity involved with this operation varies according to the different series published, with highly variable incidence rates (Table 1). A review of published studies including 409 donors and 12 sites showed that the incidence of complications can range from 0% to 67%, with a mean rate of 31% [63]. The most common complications in living donors are related to biliary system problems. Biliary fistulas can lead to collections developing adjacent to the resection line, usually resolving with conservative treatment, but sometimes requiring percutaneous drainage. Stenosis of the remaining biliary system in the donor is less common, with an incidence rate of around 1%, again occasionally requiring surgery [64].

Table 1. Right hepatectomy morbidity in living donors in different published series and Hospital Clínic de Barcelona results (SHV: suprahepatic vein)

AUTHOR	YEAR	NUMBER	MORBIDITY
Marcos	2000	40	17.5%
Fan	2000	22	23%
Grewal	2001	11	9%
Trotter	2001	24	32%
Miller	2001	52	34%
Pomfret	2001	15	67%
Beavers	2001	14	64%
Bak	2001	41	22%
Ghobrial	2002	20	20%
Malagó	2003	74	40.5%
H. Clinic	2006	51	41.2%
Global: 21 (41.2%) *	**Complications H. Clinic (n = 51)**		
Surgical: 19 (37.2%)	*Biliary leak*		*15.7%)*
	Abdominal collection		*7 (14%)*
	Wound infection		*1 (2%)*
	Eventration		*1 (2%)*
	SHV thrombosis		*1 (2%)*
	Portal stenosis		*2 (2%)*
Medical: 14 (27.4%)	*Fever*		*5 (10%)*
	Pneumonia		*3 (6%)*
	Pleural effusion		*1 (2%)*
	Urine infection		*2 (4%)*
	Peripheral phlebitis		*1 (2%)*
	Horner syndrome		*1 (2%)*

CONCLUSIONS

Living kidney donation

» Renal transplantation is a life-saving procedure, and it is well documented that the utilization of grafts from live donors offers significantly better graft and patient survival compared with deceased-donor kidneys.

» The general principle is that the donor should always be left with his/her best kidney if there are differences. When both kidneys are evaluated as equal, the kidney imposing the lowest surgical risk on the recipient should be chosen.

» The risk of mortality with living donor nephrectomy is very low. Similarly, unilateral nephrectomy in a healthy person is not associated with any increased risk of kidney disease in the long term.

Living liver donation

» LDLT offers the possibility of increasing the classic indications for liver transplantation, as in the case of older-age recipients or hepatocellular carcinoma, thus increasing the total pool of donors and reducing the waiting list.

» The applicability of living liver donation is low, with only less than one third of recipients having potential donors, and a rate between 14-25% finally undergoing LDLT.

» The probability of graft survival and patient survival in LDLT is similar to that currently obtained with grafts from deceased donors.

One of the most important factors when determining donor suitability is estimated liver volume. Due to its larger volume, the right lobe is preferred for transplant into adult recipients. LDLT using a left graft has an increased risk of postoperative complications for the recipient, the most feared being "small-for-size" syndrome.

» The mortality rate of living donor hepatectomy reaches 0.2%. The morbidity involved with this operation can range from 0% to 67%, with a mean rate of 31%. The most common complications for living liver donors are related to biliary system problems.

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LIST OF ABBREVIATIONS

ABBREVIATION	MEANING
6MWT	six minute walking test
A1ATD	alpha-1 antitrypsin deficiency
AAT	alpha-1 antitrypsin
ABG	arterial blood gass test
ABMR	antibody-mediated rejection
ACT	activated clotting time
ADCC	antibody-dependent cellular cytotoxicity
ADPKD	autosomal dominant polycystic kidney disease
AFP	alpha-fetoprotein
AGF	acute graft failure
AHA/ACC	American Heart Association/American College of Cardiology
aHUS	atypical hemolytic uremic syndrome
AMI	acute myocardial infarction
AP	arterial pressure
ALP	alkaline phosphatase
APC	antigen-presenting cells
APG	argon plasma coagulation
ASA	aspirin
ATG	anti-thymocyte globulin
ATN	acute tubular necrosis
AZA	azathioprine
BAL	bronchoalveolar lavage
BCC	*Burkholderia cepacia complex*
BD	brain death
BIS	bispectral index
BKV	BK virus
BMI	body mass index
BNP	B-type natriuretic peptide
BOS	bronchiolitis obliterans syndrome
BP	blood pressure
BUN	blood urea nitrogen
CDC	complement-dependent cytotoxicity
CDC-XM	complement-dependent cytotoxicity crossmatch
CDI	central diabetes insipidus
CEUS	contrast-enhanced ultrasound
CF	cystic fibrosis

CHUAC . . . . . University Hospital of A Coruña
CIT . . . . . cold ischaemia time
CKD . . . . . .chronic kidney disease
CLAD . . . . . chronic lung allograft dysfunction
CMV. . . . . cytomegalovirus
CN . . . . . .calceneurin
CNI. . . . . calcineurin inhibitors
CNS . . . . . central nervous system
CO . . . . . cardiac output
COPD . . . . . chronic obstructive pulmonary disease
CPB . . . . . .cardiopulmonary bypass
CS . . . . . .corticosteroids
CsA . . . . . .cyclosporine
CTA . . . . . computed tomography angiography/CT angiography
CTL . . . . . .cytotoxic T lymphocytes
CTLA . . . . . cytotoxic T lymphocyte antigen
CTP . . . . . Child-Turcotte-Pugh
CVP . . . . . central venous pressure
DAPT . . . . . .drug antiplatelet therapy
DBD. . . . . donor/donation after brain death
DCD. . . . . donation after circulatory/cardiac death
DCU. . . . . colour Doppler ultrasound
DD . . . . . deceased donor
DLCO. . . . . diffusing capacity for carbon monoxide
DM. . . . . .diabetes mellitus
DSA . . . . . donor-specific alloantibodies
dynes/sec/cm-5. . . . . measurement of pulomonary vascular resistance
EBV . . . . . Epstein-Barr virus
ECC . . . . . extracorporeal circulation
ECG . . . . . electrocardiogram
ECLS . . . . . .extracorporeal life support
ECMO . . . . . .extracorporeal membrane oxygenation
EGD . . . . . esophagogastroduodenoscopy
ELISPOT . . . . . enzyme-linked immunosorbent spot
ELTR . . . . . .European Liver Transplant Registry (organisation)
EMB. . . . . .endomyocardial biopsies
ERCP . . . . . endoscopic retrograde cholangiopancreatography
ESLD . . . . . .end-stage liver disease
ESRD . . . . . .end-stage renal disease
$EtCO_{Burkholderia}$. . . . . end-tidal carbon dioxide
EVLP . . . . . ex vivo lung perfusion

FAP . . . . . Familial amyloidotic polyneuropathy
FC-XM . . . . . (lymphocyte) flow cytometry
FEF . . . . . forced
FEV_1 . . . . . airflow obstruction
FFP . . . . . fresh frozen plasma
FHF . . . . . fulminant hepaic failure
FiO_2 . . . . . fraction of inspired oxygen
FKBP . . . . . FK506-binding protein
FRC . . . . . functional reserve capacity
FSGS . . . . . focal segmental glomerulosclerosis
GAD . . . . . glutamic acid decarboxylase
GC . . . . . glucocorticoids
GFR . . . . . glomerular filtration rate
GGT . . . . . gamma-glutamyltransferase
GRWR . . . . . graft-to-recipient weight ratio
GSD . . . . . glycogen storage disease
GVD . . . . . graft vascular disease
HAV . . . . . hepatitis A virus
HBP . . . . . high blood pressure
HBsAg . . . . . hepatitis B surface antigen
HBV . . . . . hepatitis B virus
HCC . . . . . hepatocellular carcinoma
HCT . . . . . hct (hematocrit)
HCV . . . . . hepatitis C virus
HES . . . . . hydroxyethyl starch
HF . . . . . heart failure
HFOV . . . . . high frequencyoscillatory ventilation
HFSS . . . . . heart failure survival score
HLA . . . . . human leukocyte antigen
HPS . . . . . hepato-pulmonary syndrome
HRS . . . . . hepato-renal syndrome
HT . . . . . heart transplant
HTN . . . . . hypertension
HUS . . . . . haemolytic uremic syndrome
IABP . . . . . intra-aortic balloon pump
IBP . . . . . invasive blood pressure
IC . . . . . intensive care
ICD . . . . . implantable cardioverter-defibrillator
ICP . . . . . intracranial pressure
ICU . . . . . intensive care unit
IDDM . . . . . insulin-dependent diabetes mellitus

IL-2r . . . . . Il2 receptor
ILD . . . . . Interstitial lung disease
IMPDH . . . . . inosine monophosphate dehydrogenase
INR . . . . . international normalized ratio
INVOS . . . . . regional brain oxygen saturation (brand name)
IPAH . . . . . idiopathic pulmonary artery hypertension
IPF . . . . . idiopathic pulmonary fibrosis
IR . . . . . immune resonse
ISHLT . . . . . International Society for Heart and Lung Transplantation
IT . . . . . induction therapy
IV . . . . . intravenous
IVC . . . . . inferior vena cava
IVIG . . . . . intravenous immunoglobin
IVIG . . . . . intravenous
IVUS . . . . . intravascular ultrasound
KIR . . . . . killer inhibitory receptors
KT . . . . . kidney transplantation
LA . . . . . left atrium
LAM . . . . . lymphangioleiomyomatosis
LD . . . . . living donation
LDKT . . . . . living-donor kidney transplantation
LDLT . . . . . living-donor liver transplantation
LGS . . . . . low glucose susped
LPD . . . . . Lymphoproliferative disorders
LVEF . . . . . left ventricular ejection fraction
LVTDP . . . . . left ventricle telediastolic pressure
M. tb . . . . . Mycobacterium tuberculosis
MAC . . . . . membrane attack complex
MAPI . . . . . Maryland Aggregate Pathology Index
MELD . . . . . Model for End-Stage Liver Disease
MFS . . . . . mycophenolate sodium
MHC . . . . . major histocompatibility complex
MMF . . . . . mycophenolate mofetil
MODY . . . . . maturity-onset diabetes of the young
MPA . . . . . mycophenolic acid
Mpap . . . . . mean pulmonary arterial pressure
MRSA . . . . . methicillin-resistant Staphylococcus aureus
mTOR . . . . . mammalian target of rapamycin
MUF . . . . . modified ultrafiltration
NA . . . . . noradrenaline
NAFLS . . . . . nonalcoholic fatty liver disease

NET . . . . . neuroendocrine tumours
NFAT . . . . . .nuclear factor of activated T cells
NIRS . . . . . .near-infrared spectroscopy
NK . . . . . .naturall killer cells
NMR . . . . . .nuclear magnetic resonance
NSAIDs . . . . . non sterioid anti-inlfammatory drugs
NSIP. . . . . .nonspecific interstitial pneumonia
OB . . . . . obliterative bronchiolitis
OGTT. . . . . oral glucose tolerance test
OKT3 . . . . . muromonab-CD3
ONT. . . . . .Spanish national transplant organization
P/F ratio . . . . . .PaO_2/FiO_2 ratio
PAC . . . . . pulmonary atery catheter
PAK . . . . . .pancreas after kidney transplant
pAMR . . . . . pathology antibody-mediated rejection
PAP . . . . . .pulmonary arterial pressure
PBC . . . . . .primary biliary cirrhosis
PCI. . . . . .percutaneous coronary intervention
pCO_2 . . . . . .partial pressure of carbon dioxide
PEEP . . . . . .positive end-expiratory pressure
PEF . . . . . .peak expiratory flow
PELD . . . . . paediatric end-stage liver disease
PGD. . . . . primary graft dysfunction
PGE . . . . . .prostaglandin E
PH1 . . . . . primary hyperoxaluria type 1
PHT . . . . . .pulmonary hypertension
PJP . . . . . *pneumocystis jirovecii*
pmp. . . . . per million population
PPD . . . . . .purified protein derivative
PPHT . . . . . .portopulmonary hypertension
PRA . . . . . panel-reactive antibodies
PSA . . . . . .prostate-specific antigen
PSC . . . . . primary sclerosing cholangitis
PSI . . . . . proliferation signal inhibitors
PT . . . . . .prothrombin time
PTA . . . . . .pancreas transplant alone
pTLC . . . . . .predicted total lung capacity
PTLD . . . . . post-transplant lymphoproliferative disorder
PVR . . . . . .pulmonary vascular resistance
PWP. . . . . pulmonary wedge pressure
q8h . . . . . .every 8 hours

RAAS . . . . . renin-angiotensin-aldosterone system
RAI . . . . . rejection activity Index
RAS . . . . . restrictive allograft syndrome
RBC . . . . . red blood cell
rCO_2 . . . . . elimination of CO_2
RIS . . . . . rapid sequence induction
RPS . . . . . reperfusion syndrome
RSV . . . . . respiratory syncytial virus
RV . . . . . right ventricular
RVP . . . . . right ventricular pacing
SAB . . . . . single antigen bead test
SaO_2 . . . . . oxygen saturation of arterial blood
SAP . . . . . sensor-augmented insulin pump
SBA . . . . . selective bronchoaspiration
SC . . . . . sclerosing cholangitis
SHV . . . . . suprahepatic vein
SLE . . . . . systemic lupus erythematosus
SMA . . . . . superior mesenteric artery
SMCF . . . . . shift in median channel fluorescece
SNS . . . . . sympathetic nervous system
SOS . . . . . hepatic sinusoidal obstruction syndrome
SOT . . . . . solid organ transplantation
SPK . . . . . simultaneous pancreas and kidney transplant
SrO_2C . . . . . regional brain oxygen saturation
SV . . . . . systemic vasculitis
SvO_2 . . . . . mixed venous oxygen saturation
T1DM . . . . . type 1 diabetes mellitus
Tac . . . . . tacrolimus
TB . . . . . tuberculosis
TCMR . . . . . T cell mediated rejection
TCR . . . . . T cell receptor
TEE . . . . . transoesophageal echocardiogram
TEG . . . . . thromboelastography
TEM . . . . . thromboelastometry
TFG β1 . . . . . transforming growth factor beta 1
TIPS . . . . . transjugular intrahepatic portosystemic shunt
TLC . . . . . total lung capacity
TPE . . . . . therapeutic plasma exchange
TPG . . . . . transpulmonary pressure gradient
TPM . . . . . transplant procurement managment
TSC . . . . . tuberous sclerosis complex

TTE. . . . . trans-thoracic echocardiogram
Tx. . . . . transplantation
UIP. . . . . usual interstitial pneumonia
UNOS . . . . . United Network for Organ Sharing
USA . . . . . united states
VA ECLS. . . . . venoarterial extracoropreal life support
VAD . . . . . ventricular assist devices
VHH-8 . . . . . human herpesvirus 8
VO_2 max . . . . . maximum oxygen consumption
VOD. . . . . veno-occlusive disease /sysnonym for SOS
VPR . . . . . vascular pulmonary resistance
VSR . . . . . vascular systemic resitance
VUR . . . . . vesicoureteral reflux
VV ECLS. . . . . venovenous extracorporeal life support
VVP . . . . . venovenous bypass
V-XM . . . . . virtual crossmatch
VZV . . . . . varicella-zoster virus
WU. . . . . wood units (pulmonary vascular resistance)
x' . . . . . per minute
ZnT8 . . . . . zinc-transporter autoantibodies