# Allograft Rejection After Liver Transplantation: What A Clinician Needs to Know?

By

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Cairo University

2019

- Introduction
- Incidence & risk factors
- Immunological basis & Pathogenesis
- Clinical Features & Diagnosis
- Management

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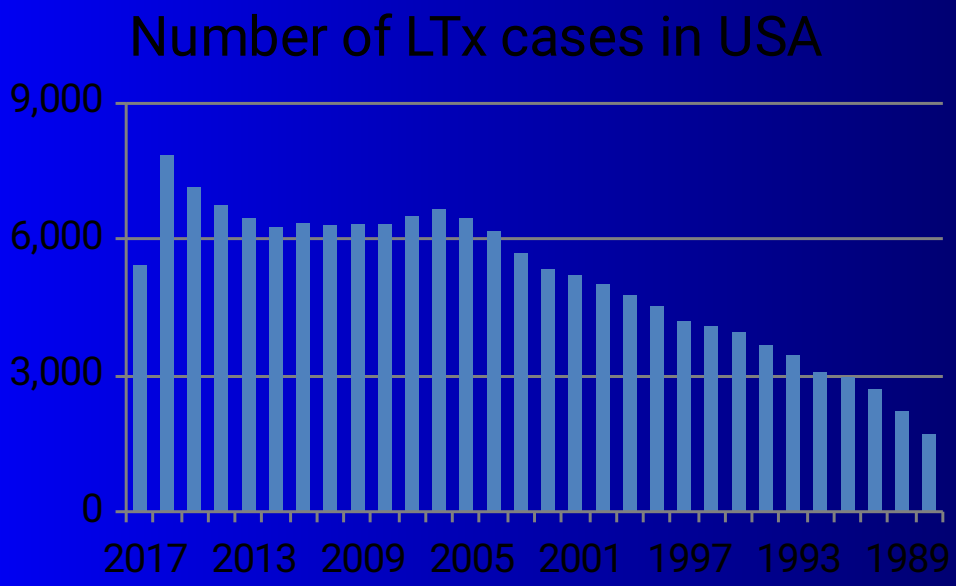
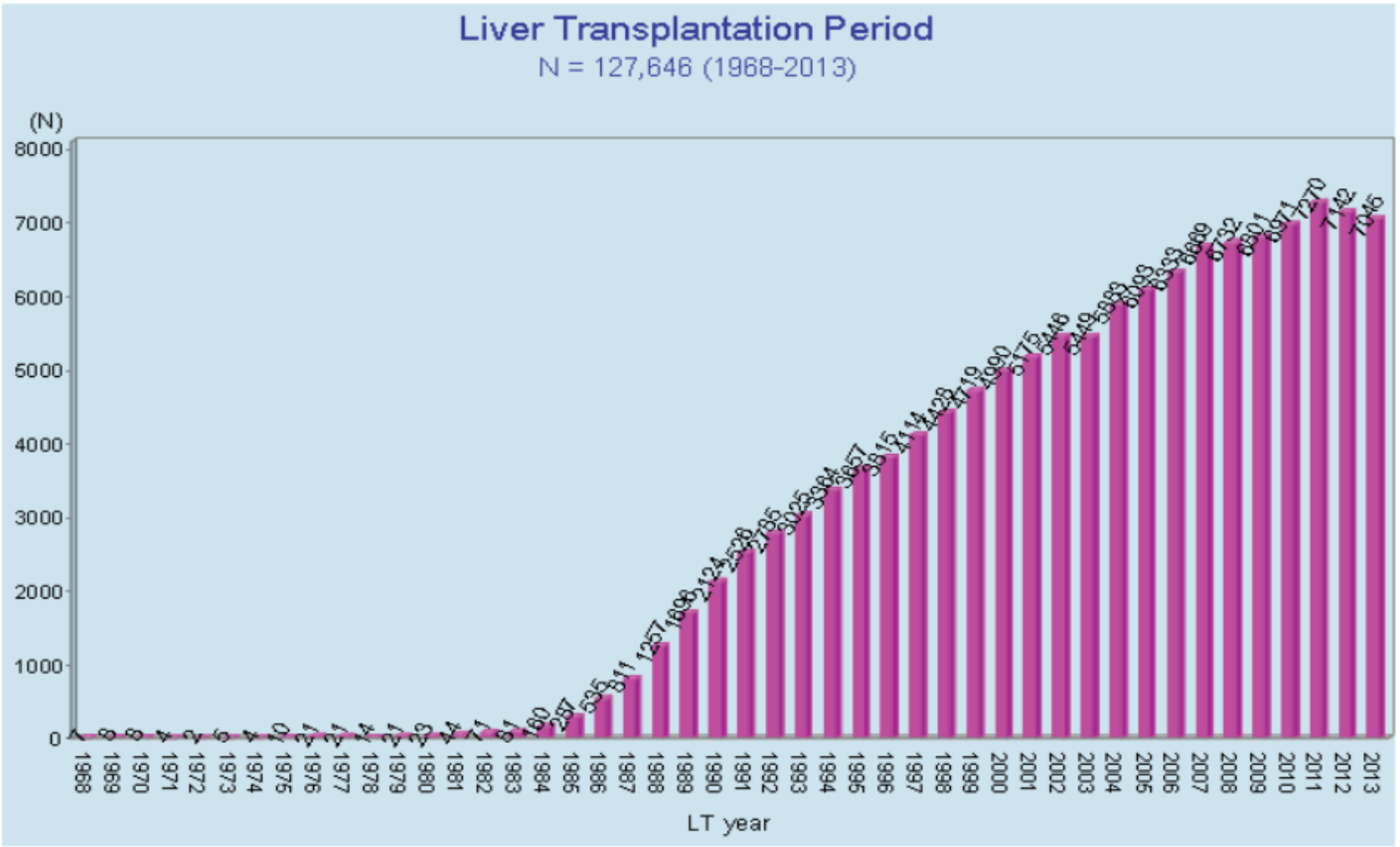
- Liver transplantation is the most effective treatment for many patients with acute or chronic liver failure resulting from a variety of causes.
- Successful LT extends life expectancy and enhances quality of life




| | Deceased Donor | Living Donor |
|---|---|---|
| To Date | 147,009 | 6,253 |
| 2017 | 5,185 | 235 |
| 2016 | 7,496 | 345 |
| 2015 | 6,768 | 359 |
| 2014 | 6,450 | 280 |
| 2013 | 6,203 | 252 |
| 2012 | 6,010 | 246 |
| 2011 | 6,095 | 247 |
| 2010 | 6,009 | 282 |
| 2009 | 6,101 | 219 |
| 2008 | 6,070 | 249 |
| 2007 | 6,228 | 266 |
| 2006 | 6,363 | 288 |
| 2005 | 6,121 | 323 |
| 2004 | 5,848 | 323 |
| 2003 | 5,351 | 322 |
| 2002 | 4,969 | 363 |
| 2001 | 4,671 | 524 |
| 2000 | 4,595 | 406 |
| 1999 | 4,499 | 258 |
| 1998 | 4,427 | 92 |
| 1997 | 4,101 | 88 |
| 1996 | 4,022 | 65 |
| 1995 | 3,880 | 54 |
| 1994 | 3,592 | 60 |
| 1993 | 3,404 | 36 |
| 1992 | 3,031 | 33 |
| 1991 | 2,931 | 22 |
| 1990 | 2,676 | 14 |
| 1989 | 2,200 | 2 |
| 1988 | 1,713 | 0 |

# Status of liver Transplantation in Europe



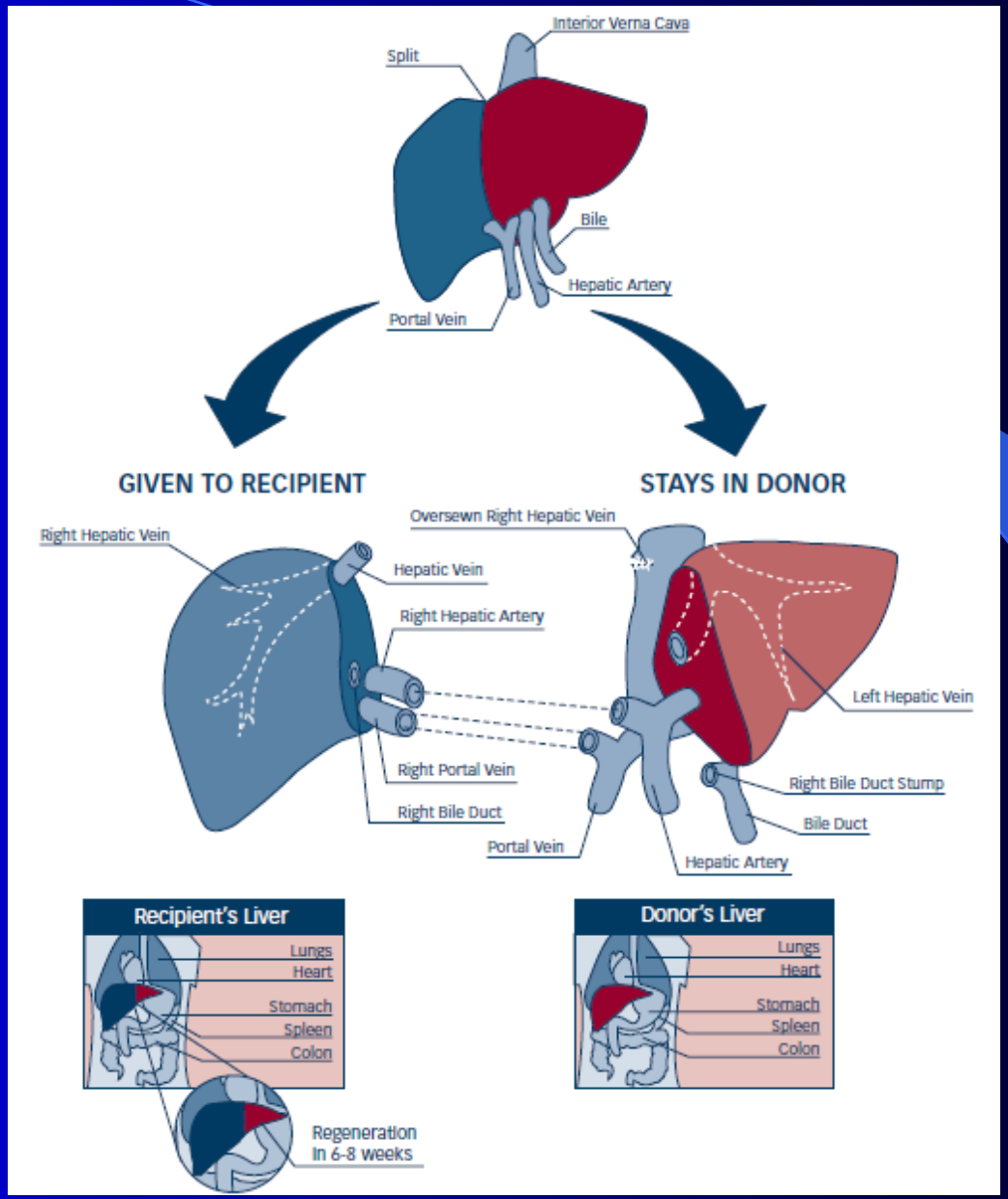

Interior Verna Cava
Split
Bile
Hepatic Artery
Portal Vein
GIVEN TO RECIPIENT
STAYS IN DONOR
Right Hepatic Vein
Hepatic Vein
Right Hepatic Artery
Right Portal Vein
Right Bile Duct
Portal Vein
Oversewn Right Hepatic Vein
Left Hepatic Vein
Right Bile Duct Stump
Bile Duct
Hepatic Artery
Recipient's Liver
Lungs
Heart
Stomach
Spleen
Colon
Regeneration
In 6-8 weeks
Donor's Liver
Lungs
Heart
Stomach
Spleen
Colon

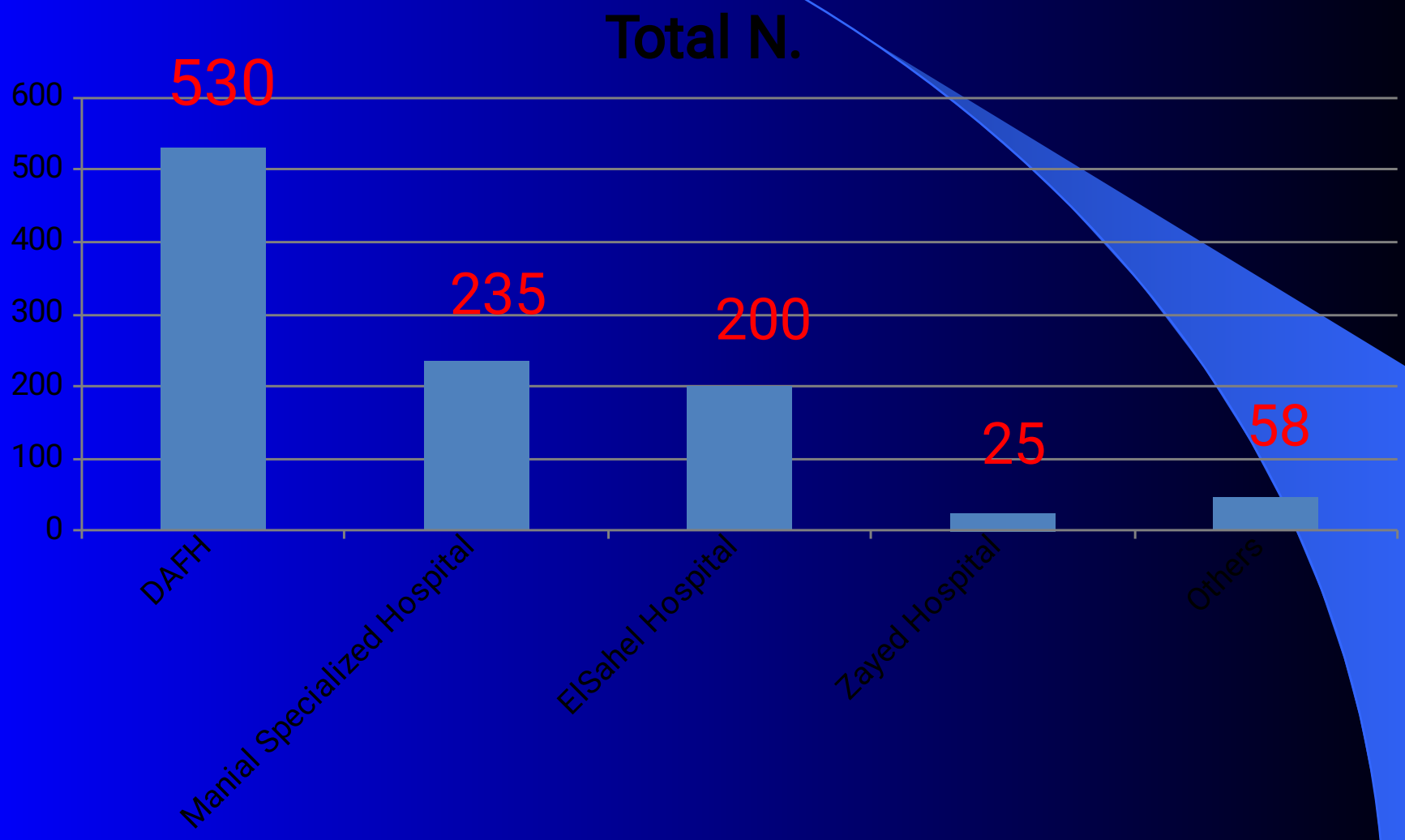
**TABLE 1.** Liver transplant activity in the Arab world until August 2013 arranged according to date of the first liver transplant

| Country | First LT | LDLT | DDLT | Total | % |
|---|---|---|---|---|---|
| Saudi | 1990 | 648 | 690 | 1,338 | 35% |
| Egypt | 1991 | 2,138 | 2 | 2,140 | 56% |
| Tunisia | 1998 | 8 | 31 | 39 | 1% |
| Lebanon | 1998 | 4 | 19 | 23 | 0.6% |
| Algeria | 2003 | 36 | — | 36 | 1% |
| Jordan | 2004 | 174 | 4 | 178 | 5% |
| Libya | 2005 | 21 | — | 21 | 0.5% |
| UAE | 2007 | 2 | — | 2 | 0.1% |
| Kuwait | 2010 | — | 2 | 2 | 0.1% |
| Iraq | 2011 | 21 | 0 | 21 | 0.5% |
| Qatar | 2011 | — | 4 | 4 | 0.1% |
| Total | | 3,052 | 752 | 3,804 | |

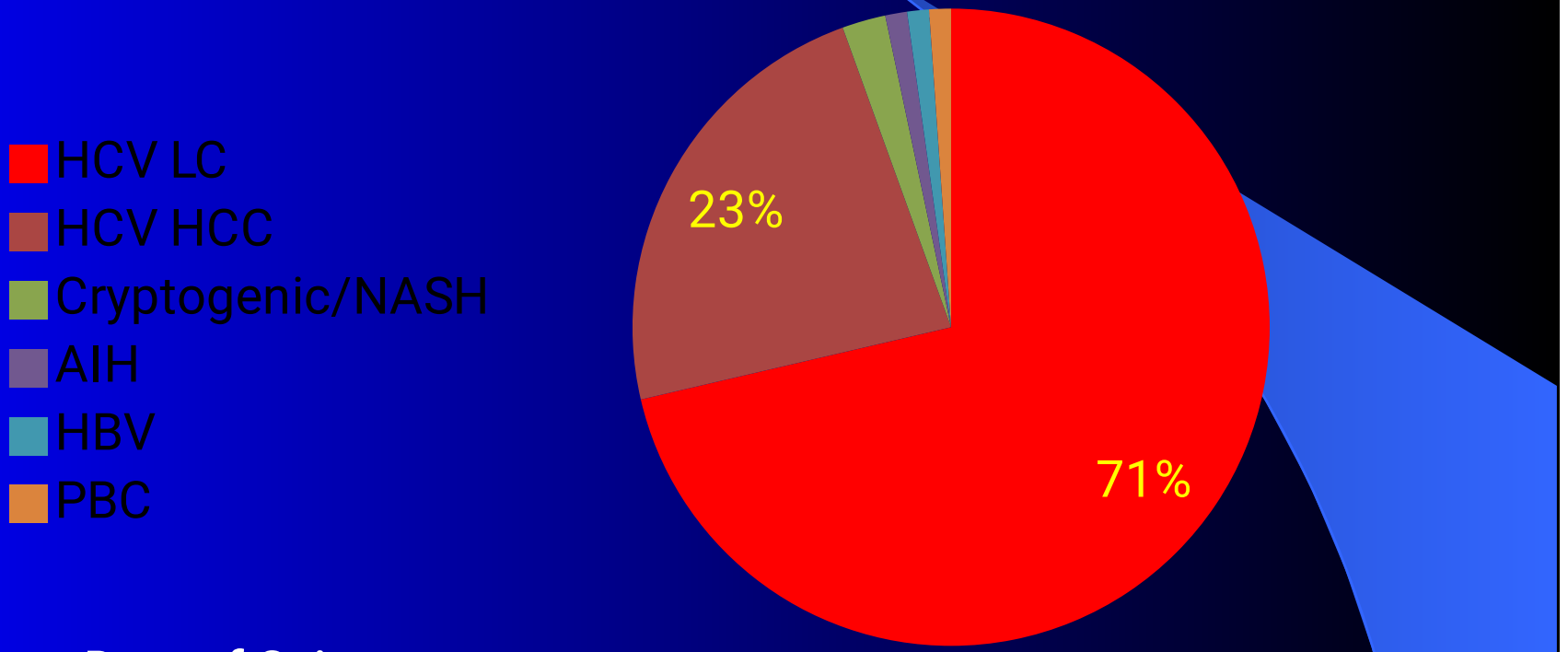
LT, liver transplantation; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; UAE, United Arab Emirates.

Khalaf H. Transplantation. 2014

# Cairo University Teams

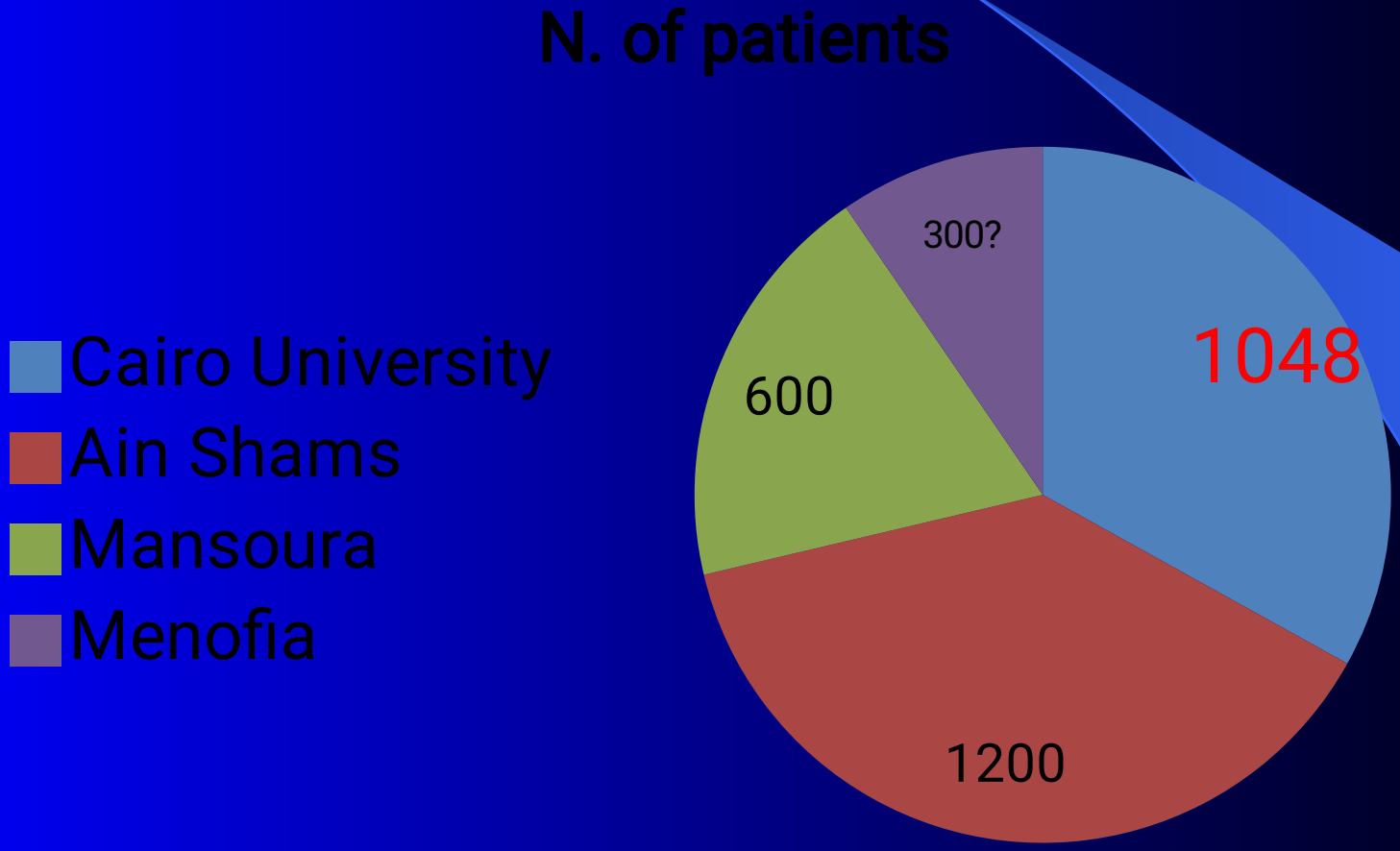


# Indications for Liver transplantation

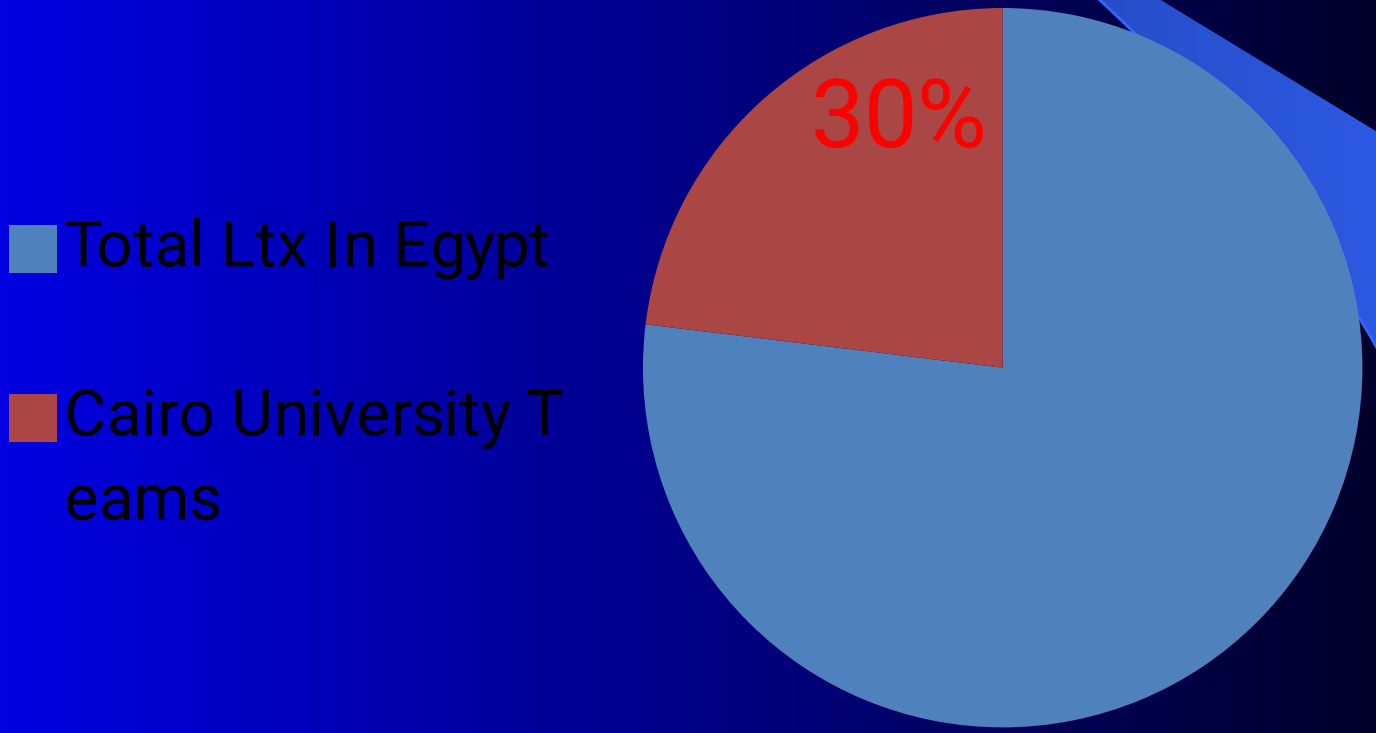



Data of Cairo
University LTx Team

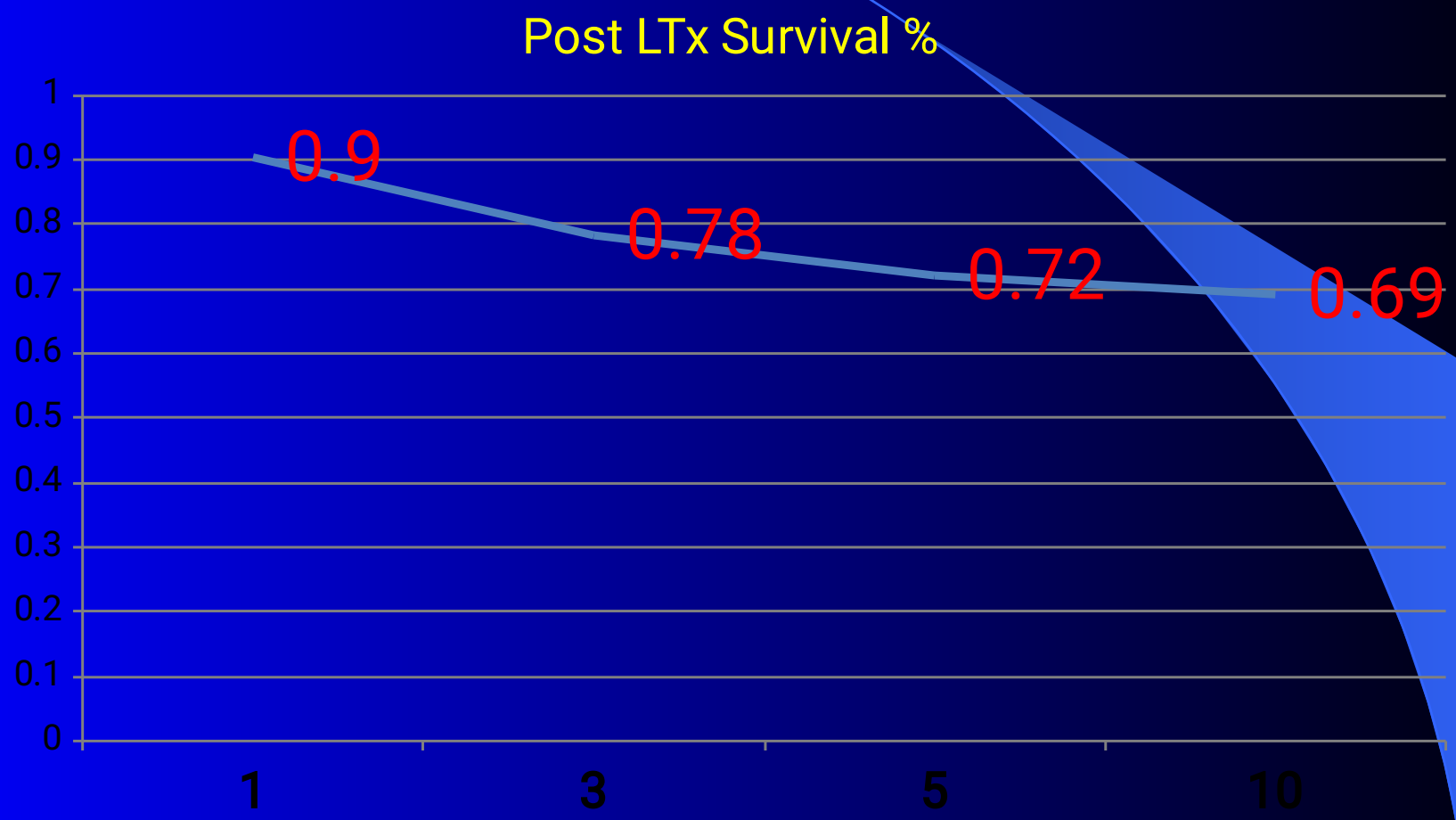
# Number of Liver Transplants by different University Teams



# *Current Total number of LTx in Egypt is approximately 3500-4000*



# Cairo University Teams



- Despite substantial technological, medical and surgical advances, liver transplantation remains a complex procedure that is accompanied by significant morbidity and mortality.
- The complications occur both immediately post-transplantation and in the long-term.

Allograft dysfunction and surgical complications occurring in the immediate postoperative period.

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**Allograft dysfunction**

- Primary non function
- Primary poor function
- Acute cellular rejection
- Recurrent viral hepatitis
- Drug hepatotoxicity

**Surgical complications**

- Postoperative hemorrhage
- Vascular complications
  - Hepatic artery thrombosis
  - Portal vein thrombosis
  - Hepatic venous obstruction
  - Other
- Biliary tract complications
  - Bile leak or fistula
  - Biliary stricture

Long-term complications

- Chronic rejection
- Renal failure
- Arterial hypertension
- Diabetes mellitus
- Dyslipidemia
- Obesity
- Bone complications
- Neurological complications
- Malignancy

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**Living donor liver transplantation *vs.* deceased liver transplantation: complications and mortality (1991–2009) – European Liver Transplant Registry** [40].

| | Living donor liver transplantation |
|---|---|
| Total number | 3622 |
| Adult LDLT (%) | 65% |
| Donor mortality rate | 0.18% |
| 5-year graft survival | 69% |
| Children | 78% |
| Adult | 63% |
| Causes of graft loss | |
| Technical complications | 26% |
| Infection | 18% |
| Rejection | 8% |
| Tumour recurrence | 12% |
| General complications | 20% |
| Non-tumour disease recurrence | 4% |

EASL 2015

# Predictors of Mortality in Living Donor Liver Transplantation

S. Elkholy[a,*], S. Mogawer[a], A. Hosny[b], M. El-Shazli[b], U.M. Al-Jarhi[a], S. Abdel-Hamed[c], A. Salah[b], N. El-Garem[a], A. Sholkamy[a], M. El-Amir[a], M.S. Abdel-Aziz[d], A. Mukhtar[e], A. El-Sharawy[f], and A. Nabil[b]

[a]Internal Medicine Department, Faculty of Medicine, Cairo University, Egypt; [b]General Surgery Department, Faculty of Medicine, Cairo University, Egypt; [c]Clinical Pathology Department, Faculty of Medicine, Cairo University, Egypt; [d]Tropical Medicine Department, Faculty of Medicine, Cairo University, Egypt; [e]Anesthesia and Intensive Care Department, Faculty of Medicine, Cairo University, Egypt; and [f]Anesthesia and Intensive Care Department, Benisuef University, Benisuef, Egypt

*Transplantation Proceedings*, 49, 1376–1382 (2017)

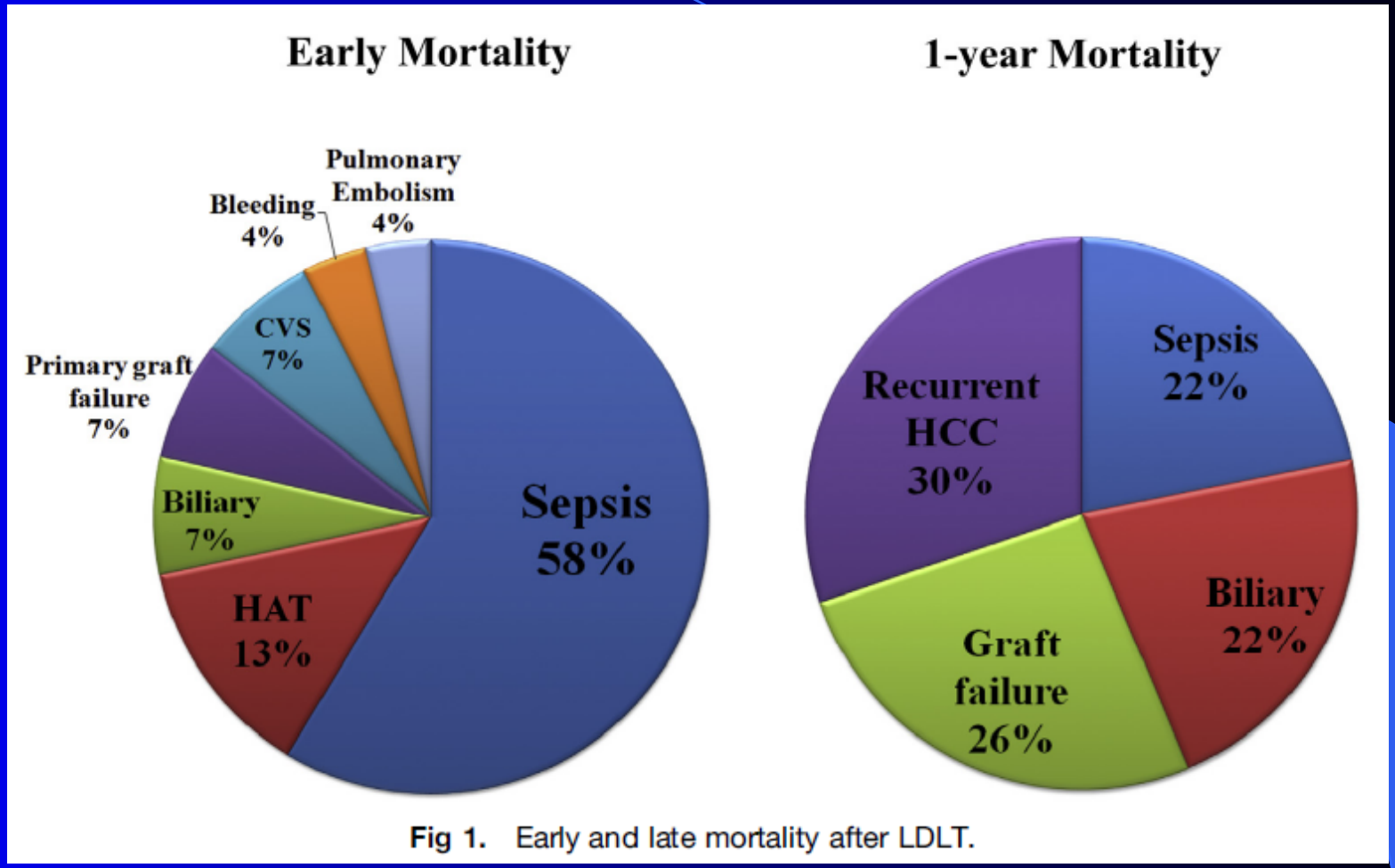


**Fig 1.** Early and late mortality after LDLT.

To conclude, sepsis is the most common cause of early mortality after LDLT. A MELD score >20, intraoperative transfusion of more than 8 units of packed RBCs, and ICU stay more than 9 days are three independent predictors of early mortality. Their incorporation into a combined risk index can be used to improve outcomes of LDLT.

- After liver transplantation (LTx), nearly every recipient will have an *elevation of injury tests (aminotransferases and/or bilirubin and alkaline phosphatase).*
- The timing, magnitude, and context of abnormal liver tests are always important considerations in determining the likely cause.

  *Andrew, et al 2016*

# CAUSES OF ELEVATED LIVER BIOCHEMISTRIES AFTER LIVER TRANSPLANTATION

**Primary Parenchymal**

*Immune*

Rejection (acute, chronic, antibody mediated)

Recurrence of autoimmune hepatitis, primary biliary cholangiopathy, primary sclerosing cholangitis

*Nonimmune*

Preservation injury, from mild to primary nonfunction

Primary infection, including procedure related, donor derived, recipient derived, and nosocomial

Recurrent infection, for example, hepatitis B and C

Drug induced, for example, secondary to antibiotics or immunosuppression

Recurrence of primary liver disease, for example, alcohol and nonalcoholic steatohepatitis

**Biliary**

Anastomotic stricture

Ischemic-type nonanastomotic strictures

Bile leak (intrahepatic or perihepatic)

Choledocholithiasis

Biliary casts, for example, following donation after cardiac death

**Other Causes**

Hemolysis

Gilbert syndrome

Space-occupying lesions, for example, posttransplant lymphoproliferative disease, recurrence of hepatocellular carcinoma, or cholangiocarcinoma

Diabetic hepatopathy

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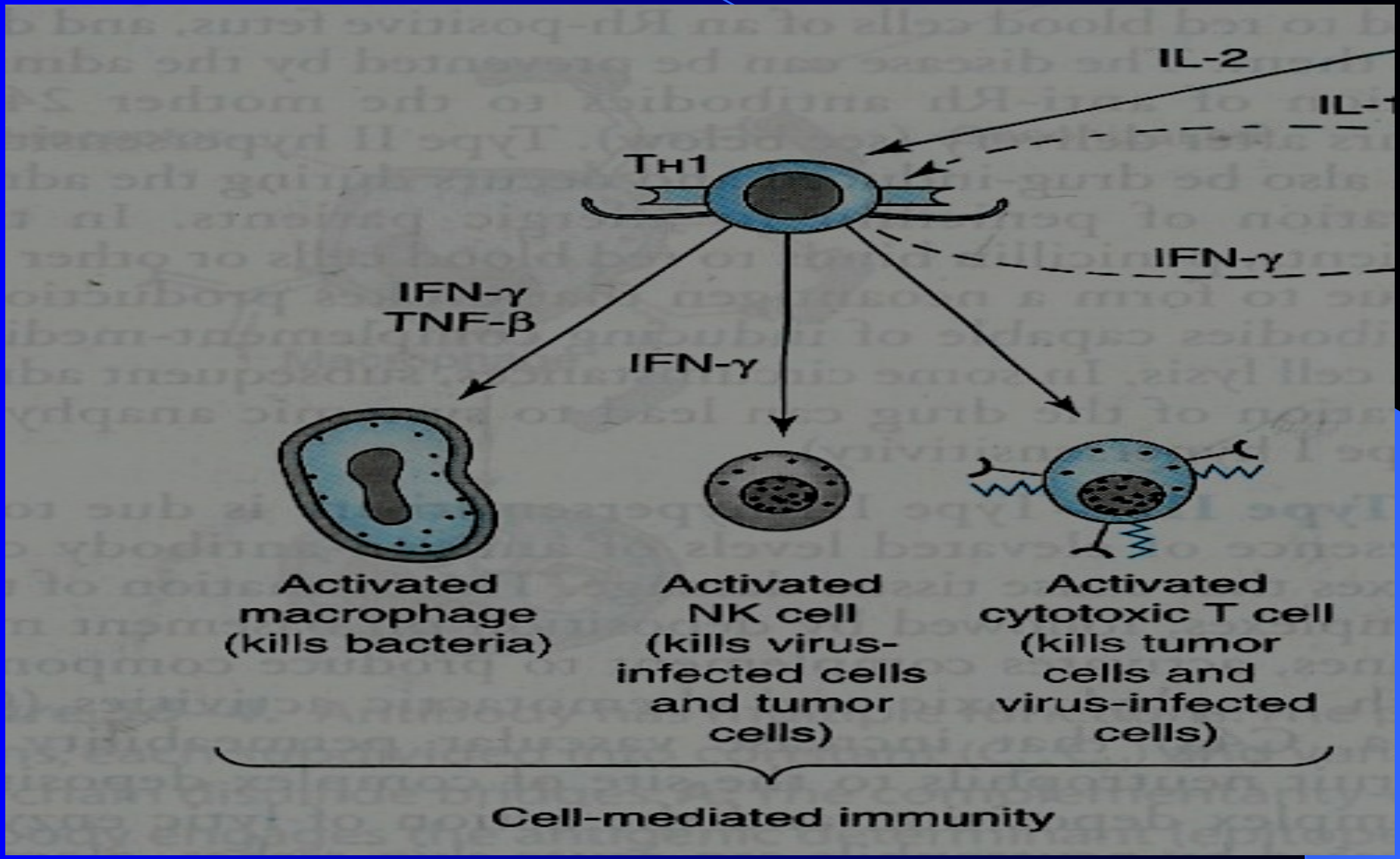
- Immune system include two main arms

1) Cell –mediated immunity.

2) Humoral (antibody–mediated  immunity

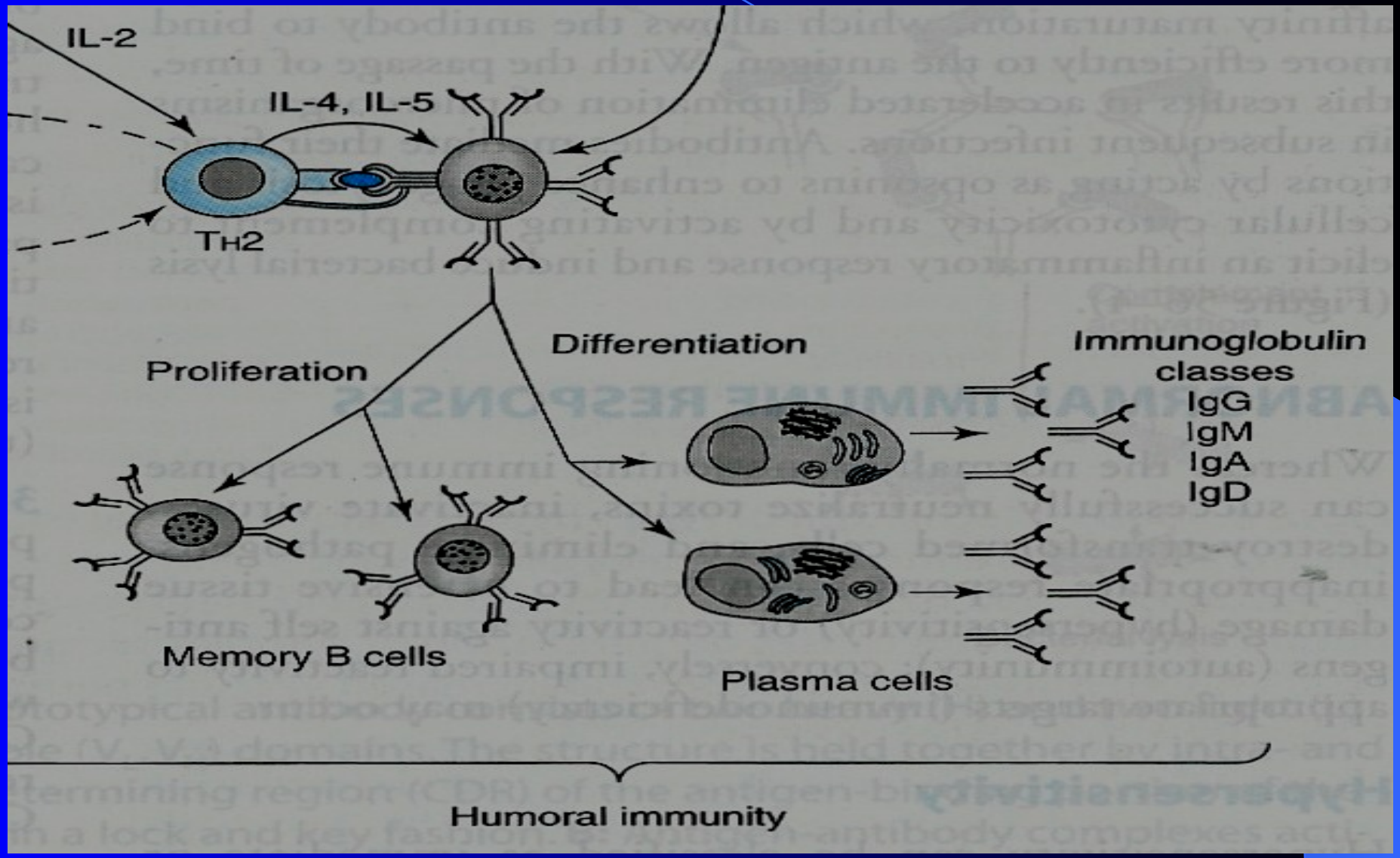
# Cell-mediated Immunity

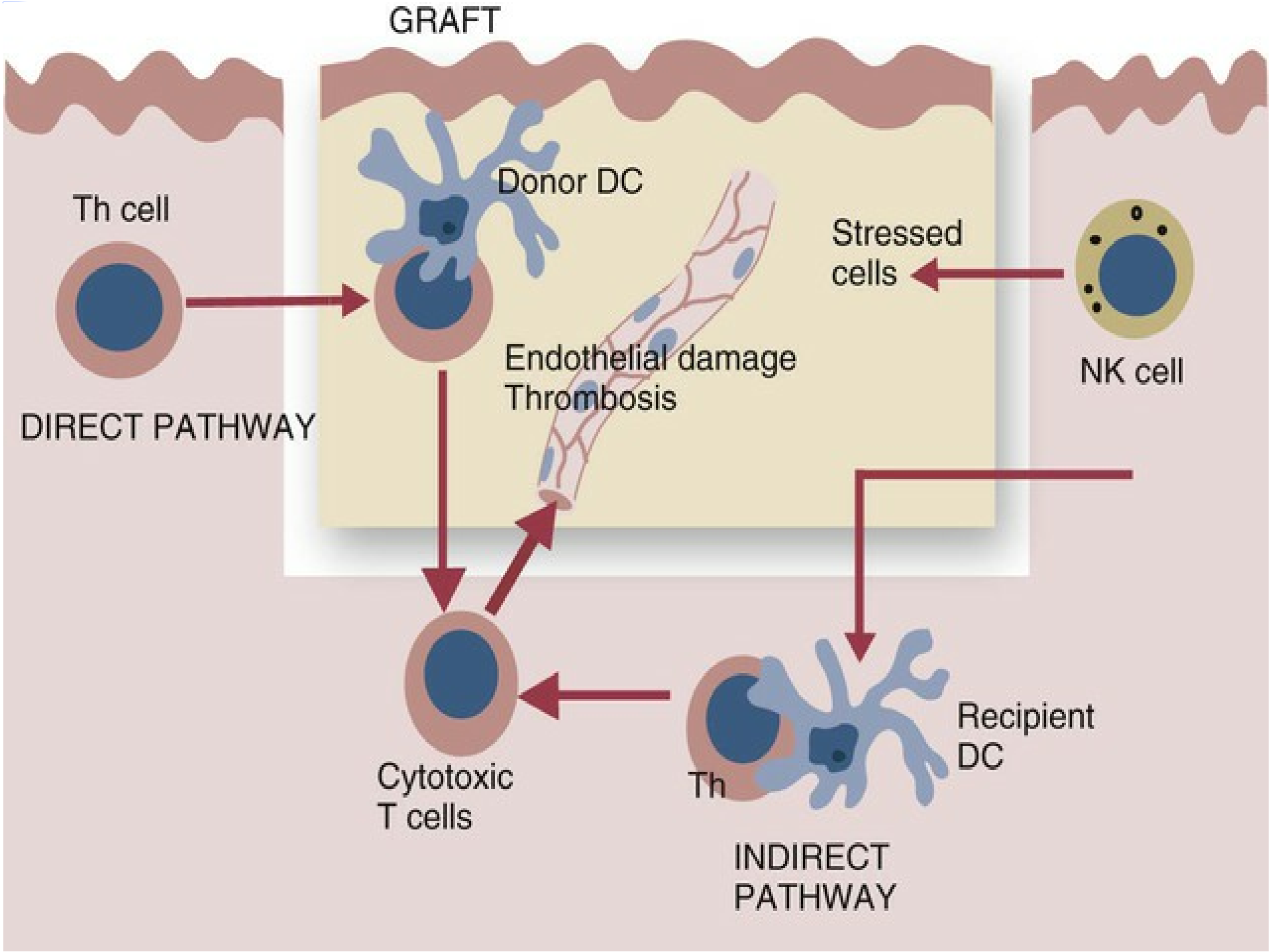


# Humoral Immunity

- B-lymphocytes TH2 produces (interleukins) IL-4 & IL-5 which in turn causes:
- B cells proliferation & differentiation into
  - memory B cells
  - Antibody secreting plasma cells

# Humoral Immunity




GRAFT
Donor DC
Th cell
Stressed
cells
NK cell
Endothelial damage
Thrombosis
DIRECT PATHWAY
Cytotoxic
T cells
Th
Recipient
DC
INDIRECT
PATHWAY

# New Concept of immunological pathways

# LIVER TRANSPLANTATION

## results in the activation of effector and immune regulatory cells

### Effector cells involved in immune-mediated liver allograft damage

- Effector T lymphocytes
- Effector B lymphocytes
- Eosinophils
- Natural killer (NK) cells

### Immune cells with graft-protecting regulatory properties

- Foxp3⁺ CD4⁺ Treg
- Myeloid regulatory cells (macrophages, DCs, MDSC)
- Foxp3⁺ CD8⁺ Treg
- Regulatory B lymphocytes
- IL-10-producing Tr1 lymphocytes
- Mesenchymal stromal cells

### Determinants of liver allograft immunogenicity

- Oxidative injury
- DAMPS (MICA/B, HMGB1, complement, ATP, heat-shock proteins)
- TLR expression
- MHC-I/II expression
- DC maturation
- Genetic background (*e.g.* autoimmune liver disease)

*Didier Samuel, et al, 2017*

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# CLINICAL FEATURES AND DIAGNOSIS OF ACUTE CELLULAR REJECTION

- Not uncommon in the first 3 months
- Symptoms of mild rejection are nonspecific:

Low-grade fever

Fatigue

Malaise

Generalized weakness

Jaundice

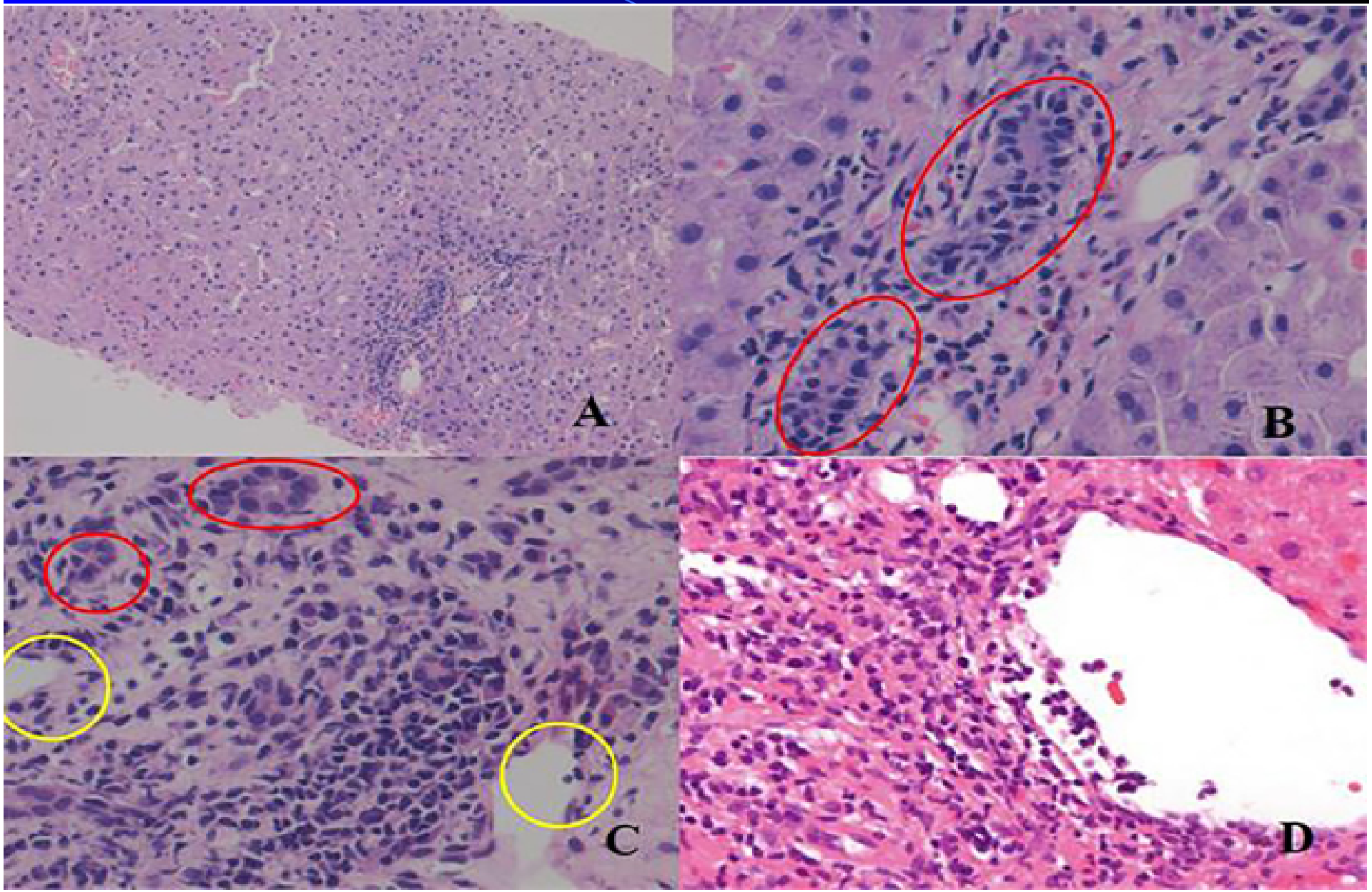
- Suspected after elevation of hepatic enzymes (serum aminotransferases, alkaline phosphatase, gamma-glutamyl transpeptidase) and/or bilirubin.
- Diagnosis depend on liver biopsy

## Differential Diagnosis of Acute and Chronic Rejection.

| Category | Etiology | Time after liver transplantation |
|---|---|---|
| Surgical issues | Hepatic artery thrombosis<br>Biliary issues | More common in early period<br>Any time |
| Infections | Cytomegalovirus, atypical viral infections | Higher chances in early months |
| Rejection | Acute cellular rejection<br>Chronic rejection (CR)<br>Antibody mediated<br>Plasma cell rich rejection | Any time after liver transplantation, majority of ACR occur early (initial 3 months)<br>CR occur late (months to years)<br>Evolving literature on antibody mediated rejection<br>Plasma cell rich rejection occurs after months to years |
| Recurrence of primary disease | Hepatitis B, hepatitis C, non-alcoholic steatohepatitis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis | Generally >1 year after liver transplantation, viral can manifest any time |

*Narendra S. 2017*

# ACR



# Banff schema

**Table 2 Rejection Activity Index for Diagnosis of ACR (from Refs. 15,24).**

| Category | Criteria | Score |
|---|---|---|
| Portal inflammation | Mostly lymphocytic inflammation involving, but not noticeably expanding, a minority of the triads | 1 |
| | Expansion of most of all of the triads, by a mixed infiltrate containing lymphocytes with occasional blasts, neutrophils and eosinophils. *If eosinophils are conspicuous and accompanied by edema and microvascular endothelial cell hypertrophy is prominent, acute antibody mediated rejection should be considered*[a] | 2 |
| | Marked expansion of most or all of the triads by a mixed infiltrate containing numerous blasts and eosinophils with inflammatory spillover into the periportal parenchyma | 3 |
| Bile duct inflammation damage | A minority of the ducts are cuffed and infiltrated by inflammatory cells andshow only mild reactive changes such as increased nuclear: cytoplasmic ratio of the epithelial cells | 1 |
| | Most or all of the ducts infiltrated by inflammatory cells. More than an occasional ductshows degenerative changes such as nuclear pleomorphism, disordered polarity and cytoplasmic vacuolization of the epithelium | 2 |
| | As above for 2, with most or all of the ducts showing degenerative changes or foacal luminal disruption | 3 |
| Venous endothelial inflammation | Subendothelial lymphocytic infiltration involving some, but not a majority of the portal and/or hepatic venules | 1 |
| | Subendothelial infiltration involving most or all of the portal and/or hepatic venules with or without confluent hepatocyte necrosis/dropout involving a minority of perivenular regions | 2 |
| | As above for 2, with moderate or severe perivenular inflammation that extends into the perivenular parenchyma and is associated with perivenular hepatocyte necrosis *involving a majority of perivenular regions* | 3 |


1. *Demetris AJ,* comprehensive update of the Banff Working Group *Am J Transpl. 2016*
2. *Banff schema for grading liver allograft rejection: an international consensus document. Hepatology. 1997*

- A score of 0–2 is no rejection
- 3 borderline (consistent with)
- 4–5 is mild
- 6–7 is moderate
- 8–9 as severe ACR.

# *LATE ONSET ACUTE CELLULAR REJECTION (LAR)*

- 3–6 months after transplantation
- LAR generally occurs at the time of cessation of initial higher immunosuppression.
- Incidence ranged from 7% to 40%.
- Causes graft loss, decreased patient survival, CR and worse prognosis.
- Low mean trough Tacrolimus levels preceded

- more common in autoimmune etiology before liver transplant.
- The LAR was more common in females and younger recipients.
- Differential diagnosis of LAR is plasma cell rich rejection (de novo autoimmune hepatitis or DAIH)

# *CLINICAL FEATURES AND DIAGNOSIS OF CHRONIC REJECTION*

- occurs months to years after liver transplantation
- no time limit is intended in definition
- CR occurs in 3–17%
- The incidence of CR is lower in Tacrolimus compared to Cyclosporin.

- CR is characterized by obliterative arteriopathy and ductopenia
- Presents with progressive cholestatic graft dysfunction and may results graft loss

## Early Versus Late CR

| Parameter | Early CR *(at least 2 findings should be present)* | Late CR *(at least 2 findings should be present)* |
|---|---|---|
| Small bile ducts (<60 μm) | Senescence-related changes involving a majority of ducts; bile duct loss | Degenerative changes in remaining bile ducts, loss in ≥50% of portal tracts |
| Terminal hepatic venules and zone 3 hepatocytes | *Perivenular mononuclear inflammation*<br>Lytic zone 3 necrosis and inflammation<br>Mild perivenular fibrosis | Focal obliteration<br>Variable inflammation<br>Moderate to severe (bridging) fibrosis |
| Portal tract hepatic arterioles | Occasional loss involving <25% of portal tracts | Loss involving >25% of portal tracts |
| Large perihilar hepatic artery branches | Intimal inflammation, focal foam cell deposition without lumenal compromise | Lumenal narrowing by subintimal foam cells<br>Fibrointimal proliferation |
| Large perihilar bile ducts | Inflammation damage and focal foam cell deposition | Mural fibrosis |
| Other | So-called "transition" hepatitis with spotty necrosis of hepatocytes | Sinusoidal foam cell accumulation; marked cholestasis |

*Demetris AJ, Am J Transpl. 2016*

## Terminology Updates

| Older (discouraged) terminology | Newer (preferred) terminology |
|---|---|
| Humoral rejection | Antibody-mediated rejection (AMR) |
| (Acute) cellular rejection | T cell–mediated rejection (TCMR) |
| *De novo* auto-immune hepatitis | Plasma cell rich–rejection |
| Plasma cell hepatitis | |

*Demetris et al, 2016*

# *Plasma cell–rich rejection (de novo autoimmune/plasma cell hepatitis)*

- Atypical presentations
- poorly understood and uncommon (3–5% of recipients)
- late (>6 months) dysfunction that resembles native liver autoimmune hepatitis (AIH)

# Characteristics of plasma cell–rich rejection

- More prevalent and severe lymphocytic cholangitis.
- IgG4+ plasma cell over-representation >50% vs. 3% - AIH
- More aggressive central perivenulitis
- DSA+/ classical and other autoantibodies
- Portal microvascular C4d deposition
- Co-existent typical TCMR or chronic rejection features in 18–24% of cases

Criteria for the diagnosis of plasma cell–rich rejection[1,2]

Must fulfill criteria 1 and 3; criterion 2 is desirable, but not absolutely required:

(1) Portal and/or perivenular plasma cell–rich (estimated >30%) infiltrates with easily recognizable periportal/interface and/or perivenular necro-inflammatory activity usually involving a majority of portal tracts and/or central veins. Most of these cases are graded at least "moderate" with a total RAI score ≥5 because "V score" is usually "3" because of aggressive perivenular activity, whereas "Portal Inflammation" score is usually ≥2.

(2) Lymphocytic cholangitis is usually present and a desirable feature, but not absolutely required (inflammatory bile duct damage might be a relatively minor component, but Banff component score for bile duct injury is usually ≥1).

(3) Original disease other than autoimmune hepatitis.

*Demetris et al, 2016*

# *Antibody-Mediated Rejection (AMR)*

- (AMR) in liver transplants is a field in its infancy compared with kidney and lung
- First several weeks after transplantation in highly sensitized recipients.
- Graft dysfunction/hyperbilirubinemia, thrombocytopenia low serum complement levels
- Post-transplant DSA persistence.
- Circulating immune complexes.

Criteria for establishing the diagnosis of acute AMR in liver allografts

Definite for acute/active[1] AMR (all four criteria required):

(1) Histopathological pattern of injury consistent with acute AMR, usually including the following: portal microvascular endothelial cell hypertrophy, portal capillary and inlet venule dilatation, monocytic, eosinophilic, and neutrophilic portal microvasculitis, portal edema, ductular reaction; cholestasis is usually present, but variable; edema and periportal hepatocyte necrosis are more common/prominent in ABO-incompatible allografts (57,117,139); variable active lymphocytic and/or necrotizing arteritis.

(2) Positive serum DSA.

(3) Diffuse (C4d score = 3) microvascular C4d deposition[1] on frozen or formalin-fixed, paraffin-embedded tissue in ABO-compatible tissues or portal stromal C4d deposition in ABO-incompatible allografts.

(4) Reasonable exclusion of other insults[1] that might cause a similar pattern of injury (see text). Most cases will score (C4d-score: 3+ h-score = 5 or 6; see below).

*Demetris et al, 2016*

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# ACR / TCMR

Dogan et al. 2018

Dependent and independent risk factors associated with acute graft rejection

| Variable | Univariate (p-value) | Multivariate* (p-value) | OR (95% CI) |
|---|---|---|---|
| Biliary complications | 0.005 | 0.001 | 4.89 (2.00–11.98) |
| CMV mismatch R+ status | 0.082 | 0.034 | 9.88 (1.18–82.36) |
| Sex mismatch | 0.069 | 0.010 | 3.16 (1.31–8.10) |
| Sex mismatch with female donor | 0.115 | 0.034 | 3.0 (1.10–7.58) |
| Recipient age | 0.032 | 0.065 | 1.0 (0.96–1.04) |
| CMV mismatch D+ status | 0.274 | – | – |
| Sex mismatch with male donor | 0.560 | – | – |
| Donor age | 0.530 | – | – |
| Donor sex | 0.900 | – | – |
| Cold ischemia time | 0.476 | – | – |
| Warm ischemia time | 0.875 | – | – |
| Recipient sex | 0.597 | – | – |
| Hepatitis C | 0.986 | – | – |
| Hepatitis B | 0.818 | – | – |
| Autoimmune hepatitis | 0.6955 | – | – |
| Hepatocellular carcinoma | 0.286 | – | – |
| Cholestatic liver disorders | 0.732 | – | – |
| MELD score | 0.922 | – | – |
| Number of LTs | 0.04 | 0.296 | 1.7 (0.62–4.77) |
| Pre-transplant diabetes mellitus | 0.286 | – | – |
| Post-transplant diabetes mellitus | 0.408 | – | – |
| Immunosuppression regimen after LT | 0.755 | – | – |

## *ACR / TCMR*

- Autoimmune etiology of underlying liver disease before liver transplantation (PBC, PSC,AIH)
- Cytomegalovirus infection
- Low levels or noncompliance to immunosuppression
- Positive lymphocyte cross-match
- Lower recipient age
- Donor-recipient ethnic origin
- Male donor into female recipient
- Higher donor age
- Higher cold ischemia time

# CR

- In addition to previously mentioned factors;

1. Higher number and severity of acute rejection episodes
2. Retransplantation for CR
3. Male donor into female recipient
4. Higher donor age
5. Higher cold ischemia time
6. Genetically unrelated donors when compared to genetically related donors in LDLT

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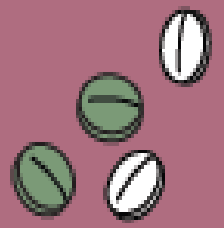
# CONVENTIONAL NON-SPECIFIC IMMUNOSUPPRESSION



## Steroids and anti-metabolites
(azathioprine, mycophenoylic acid)

- √ Reduce/delay the administration of calcineurin inhibitors to reduce nephrotoxicity
- X Not as monotherapy

## Calcineurin inhibitors
(cyclosporin A, tacrolimus)

- X Leads to off-target toxicit
- √ Prevent acute cellular rejection
- √ Mainstay immuno-suppressants

## mTOR inhibitors
(sirolimus, everolimus)

- √ Anticancer properties, reduced nephrotoxicity from calcineurin inhibitors
- X Other side effects

## Antibodies
(basiliximab, thymoglobulin, campath-1H)

- √ Induction therapy during the first hours to reduce/ delay the administration of calcineurin inhibitors

*Didier Samuel, 2017*

# *Prevention*

- Immunosuppression regimens consisting of Tacrolimus with MMF or an mTOR inhibitor are highly effective in preventing acute rejection after LT.
- Higher rejection rate with immunosuppression regimen consisting of cyclosporine and prednisolone with or without azathioprine

# IMMUNOMONITORING STRATEGIES

**Aim to:**

1) Stratify recipients according to their immunological risk pre- and post-transplantation

2) Identify rejection/graft damage before it becomes clinically apparent

3) Detect over immunosuppression

4) Identify tolerant recipients

*Didier Samuel, 2017*

# NOVEL IMMUNOTHERAPEUTIC APPROACHES

## CELL-BASED APPROACHES

- Adoptive transfer of *ex vivo* expanded immune regulatory cells
- Stem cell therapy to achieve hematopoietic chimerism
- Promotion of endogenous immune regulatory cell function and/or expansion

## TARGETED IMMUNOTHERAPIES

- Inhibiting inflammatory cytokines
- Inhibiting T and B cell signaling
  (bortezomib, JAK & PKC inhibitors)
- B and T cell depletion
  (rituximab, cyclophosphamide)
- Complement inhibition
- Co-stimulation blockade
  (belatacept, anti-CD28, anti-CD40, anti-ICOS)

## APPROACHES TO REDUCE LIVER ALLOGRAFT IMMUNOGENICITY

- Machine perfusion
- Targeted immunotherapies
- Cell-based immunotherapies

*Didier Samuel, 2017*

# *Treatment of ACR / TCMR*

- Most of acute rejection episodes improve with:

1. Steroid boluses (500–1000 mg of methyl-prednisolone is given for 1–3 days followed by taper
2. Escalation of immunosuppression.

- Generally it does not have adverse impact on graft or patient survival in long term.

*Goddard, Liver Transpl. 2002, Seiler CA, Transpl Int. 1999*

| Regimen B | Regimen A |
| --- | --- |
| **Methylprednisolone** | **Methylprednisolone** |
| **1000 mg/day intravenously** | 1000 mg for first day |
| **for three days followed by** | 200 mg on second day |
| **baseline dose of 20 mg on** | 40 mg every day for 5 days |
| **4th day.** | 20 mg at 7th day |
| 50% | The response 83% |
| More infections (90% ) | Less infections (55%) |

*Volpin et al , 2002, Narendra, 2017*

# *TREATMENT OF STEROID RESISTANT ACUTE CELLULAR REJECTION*

- Majority of ACR episodes improve with steroid therapy or repeat steroid therapy (infrequently needed).
- Steroid resistant ACR may happen in 10% of ACR
- Conversion to:
  - Tacrolimus, Sirolimus, Mycophenolate,
  - Anti thymocyte globulin,
  - Anti-CD3 monoclonal antibody (Muromonab CD3 -OKT3)
  - Anti interleukin 2 agents (Basiliximab -Simulect)

# *TREATMENT OF CHRONIC REJECTION*

Principle:

Escalation of immunosuppression

OR

Retransplantation in absence of response

# *Strategy*

1. Escalation of baseline immunosuppressive drugs
2. Providing additional IS drugs

- Sirolimus or Everolimus as an additional agent to immunosuppressive regimen, these agents provide additional site of action in the immunity cascade.
- Addition of mTOR inhibitors has been shown to reverse CR in approximately half of patients.

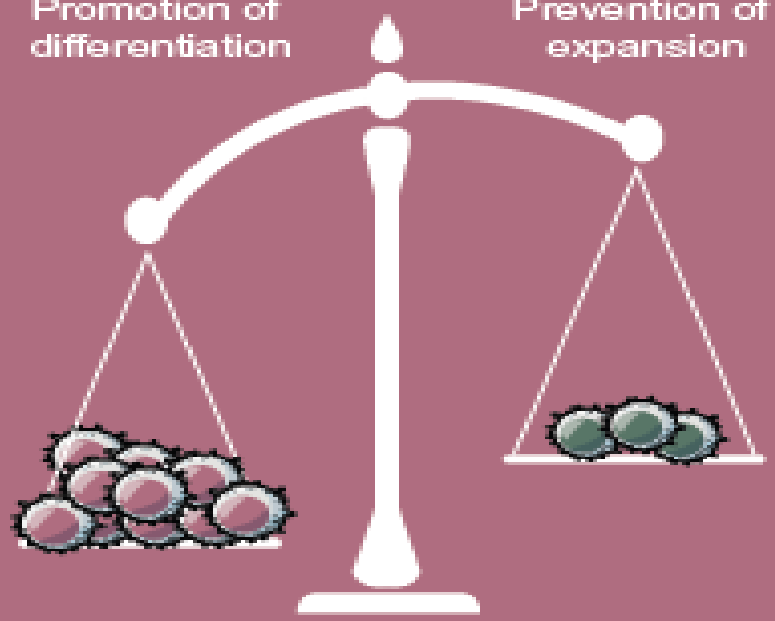
## *Predictors of non-recovery*

1. Donor age
2. More extensive bile duct loss
3. Small arterial loss
4. Higher total bilirubin and aspartate aminotransferase values.

# Transplantation tolerance

Tolerance is defined as stable graft function in a recipient who is off immunosuppressive drugs and in whom no clinically significant detrimental immune responses or immune deficits are detected.

## ↑ Graft inflammation




Teff:

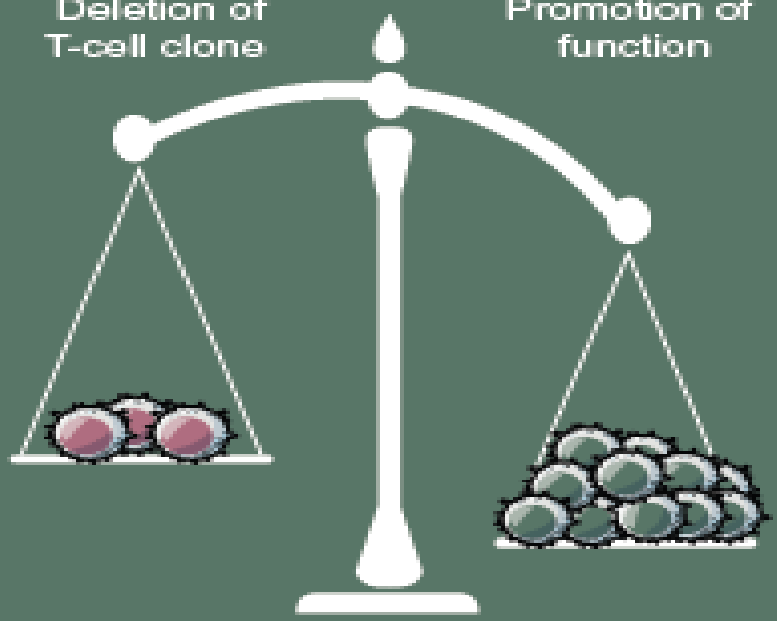
Th17, Th1, Th2

Regulatory immune cell subsets:

Treg, CD8reg, Bregs, Tol-DC, NK/NKT, MDSC

**Hightened risk of graft REJECTION**

## Tolerogenic therapies




Teff:

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**Greater graft TOLERANCE**

# Possible selection criteria for IS DC

- Time greater than 6 years since Tx.
- Absence of recent evidence of rejection.
- No history of autoimmunity.
- Liver biopsy without significant inflammatory damage
- Approximately 40% likelihood of being able to successfully discontinue immunosuppression.

*Clavien PA, Lancet Gastroenterol Hepatol 2017*

- Biomarkers of tolerance are currently being tested within prospective clinical trials.
- In addition, the use of immunomodulatory cell therapy is a promising strategy to intentionally induce tolerance shortly after transplantation.

*Mastoridis S, Curr Opin Organ Transplant 2016*

# Take Home Messages

- ACR and CR present as graft dysfunction and a liver biopsy is needed for definitive diagnosis.
- Early ACR does not affect graft survival, late ACR is associated with inferior graft survival as compared to early ACR and may evolve into CR.
- CMV infection, Low levels or noncompliance to immunosuppression and others are risk factors for rejection.
- Most of ACR/TCMR respond to steroid bolus.

- CR responds to increased immuno-suppression in approximately half of cases.
- Non-responding CR is associated with high mortality in absence of retransplantation.

- Routine DSA monitoring may help IS management, but work is needed to better define the following:

1. DSA-associated tissue injury patterns.
2. Relative contribution of AMR to “mixed” TCMR and AMR episodes.
3. appropriate IS management

- Immunotherapy for organ transplantation with Tolergenic mediators is the future for better Tolerance.


The
Liver
story


THANK
YOU