Impacto de la patología del transplante en un Servicio de Anatomía Patológica.

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São Paulo – Brazil

2011

Federal University of São Paulo - UNIFESP

Nº of courses: 29

Nº of Campi: 5

Nº of Hospitals: 6

- Hospital São Paulo (1061 beds)
- Hosp. Clín. Luzia de Pinho e Melo (282 beds)
- Hospital Estadual de Diadema (262 beds)
- Hospital Geral de Pirajussara (299 beds)
- Hosp. Mun. Ver. José Storopolli (205 beds)

Hospital do Rim e Hipertensão
(Kidney & Hypertension Hospital)
(143 beds)

Hospital do Rim e Hipertensão

(Kidney & Hypertension Hospital)

Funded in 1998
Division of Nephrology of the Federal University of São Paulo (UNIFESP)

Mission: Education, research and care for the prevention and treatment of hypertension and kidney diseases

- 143 beds
- 127 beds (ward)
- 16 beds- ICU
- 4 surgical rooms
- 731 employees

ANNUAL NUMBER OF RENAL TX UNIFESP

Total number of renal graft biopsies in our Service

Period: 2008 – 2011

Total number of graft biopsies: 6638

Total number of biopsies from donors: 1250

Total number of biopsies: 7338

Renal biopsy is an invasive procedure!

Then:

- Look for a diagnosis!
- Get 2-3 long “cores” (needle 16-18 gauge)
  - Sensitivity for one “core” = 90%
  - Sensitivity for two “cores” = 99%
- Techniques:
  - **Optical microscopy**
  - **Immunofluorescence**
    - **C4d**
    - Tubular HLA-DR
    - Immunoglobulins, C3
  - Electron microscopy – Glomerulopathy- > 12 months after-transplantation

Clinical value of the renal graft biopsy:

- 30-60% of the patients will develop graft dysfunction
- Biopsy features:
  - Change the clinical diagnosis in 38% of the cases[1]
  - Change treatment in 83% of the cases[2]
  - Avoid unnecessary immunossupressive treatment in 40% of the cases[3]

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1. WALTZER et al., Transplantation 43:100, 1987
2. KISS et al., Clin Nephrol 8:132, 1992
3. MATAS et al., Surgery 98:922, 1985

Banff Classification – 2009 - Update

Table 1: Banff 97 diagnostic categories for renal allograft biopsies—Banff '09 update

1. Normal
2. Antibody-mediated changes (may coincide with categories 3, 4 and 5 and 6)
   Due to documentation of circulating antidonor antibody, C4d,[1] and allograft pathology

C4d deposition without morphologic evidence of active rejection

C4d+, presence of circulating antidonor antibodies, no signs of acute or chronic TCMR or ABMR (i.e. g0, cg0, ptc0, no ptc lamination (<5 layers by electron microscopy), no ATN-like minimal inflammation). Cases with simultaneous borderline changes are considered as indeterminate

Acute antibody-mediated rejection[2]

C4d+, presence of circulating antidonor antibodies, morphologic evidence of acute tissue injury, such as (Type/Grade)
I. ATN-like minimal inflammation
II. Capillary and or glomerular inflammation (ptc/g >0) and/or thromboses
III. Arterial – v3

Chronic active antibody-mediated rejection[2]

C4d+, presence of circulating antidonor antibodies, morphologic evidence of chronic tissue injury, such as glomerular double contours and/or peritubular capillary basement membrane multilayering and/or interstitial fibrosis/tubular atrophy and/or fibrous intimal thickening in arteries

3. Borderline changes: 'Suspicious' for acute T-cell mediated rejection (may coincide with categories 2 and 5, and 6)
   This category is used when no intimal arteritis is present, but there are foci of tubulitis (t1, t2 or t3) with minor interstitial infiltration (i0 or i1) or interstitial infiltration (i2, i3) with mild (t1) tubulitis
4. T-cell mediated rejection (TCMR, may coincide with categories 2 and 5 and 6)

Acute T-cell mediated rejection (Type/Grade:)
IA. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of moderate tubulitis (t2)
IB. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of severe tubulitis (t3)
IIA. Cases with mild to moderate intimal arteritis (v1)
IIB. Cases with severe intimal arteritis comprising >25% of the luminal area (v2)
III. Cases with 'transmural' arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)

Chronic active T-cell mediated rejection
'chronic allograft arteriopathy' (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima)

5. Interstitial fibrosis and tubular atrophy, no evidence of any specific etiology
   (may include nonspecific vascular and glomerular sclerosis, but severity graded by tubulointerstitial features)
   Grade
   I. Mild interstitial fibrosis and tubular atrophy (<25% of cortical area)
   II. Moderate interstitial fibrosis and tubular atrophy (26–50% of cortical area)
   III. Severe interstitial fibrosis and tubular atrophy/ loss (>50% of cortical area)
6. Other: Changes not considered to be due to rejection- acute and/or chronic (For diagnoses see table 14 in (49); may include isolated g, cg, or cv lesions and coincide with categories 2, 3, 4, and 5)

ATN, acute tubular necrosis.
The 2009 updates are underlined. All existing scoring categories (g, t, v, i, ptc, cg, ct, ci, cv, ah, mm) remain unchanged (45, 49).
[1]Please refer to Banff 2007 classification paper (45).
[2]Suspicious for antibody-mediated rejection if C4d (in the presence of antibody) or alloantibody (C4d+) not demonstrated in the presence of morphologic evidence of tissue injury.

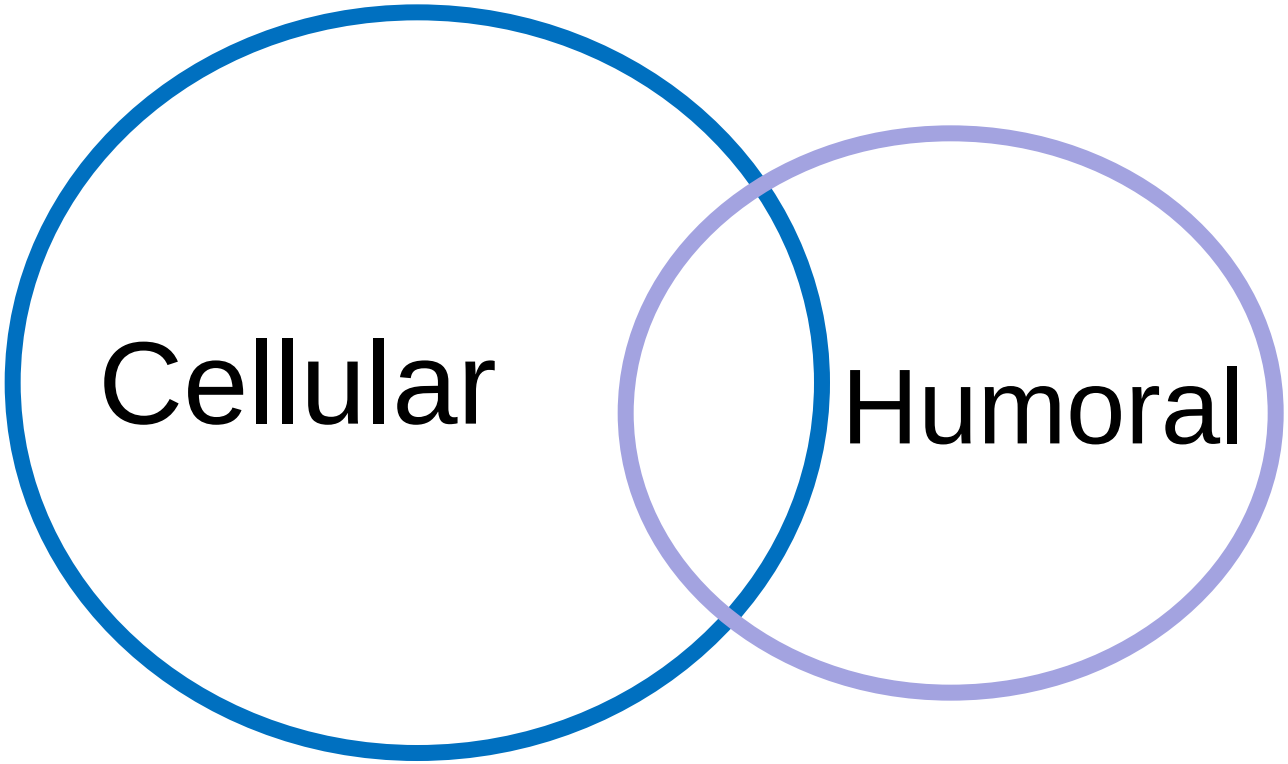
Acute humoral rejection

2. Antibody-mediated Rejection
   Rejection due, at least in part, to documented anti-donor antibody ("suspicious for" if antibody not demonstrated)
   Type (Grade)
   I. ATN-like-C4d+, minimal inflammation
   II. Capillary-margination and/or thromboses, Ig and/or C4d+
   III. Arterial - v3, C4d+

Features:

- **Morphologic**
  - Acute tubular injury
  - Neutrophils in capillaries and/or glomeruli and/or capillary thrombosis
  - Fibrinoid necrosis in arteries
- **Immunologic** → C4d in peritubular capillaries
- **Serologic** → Anti-donor antibodies

Acute Rejection: Cellular / Humoral



25% of AHR misdiagnosed by histology alone

60% of AHR assoc. with ACR

Mauiyyedi et al, JASN 13:779,2002

Cellular Rejection

Table 2. Banff 97 diagnostic categories for renal allograft biopsies - update

1. Normal, see Definitions
2. Antibody-mediated Rejection
   Rejection due, at least in part, to documented anti-donor antibody ("suspicious for" if antibody not demonstrated)
   Type (Grade)
   I. ATN-like-C4d+, minimal inflammation
   II. Capillary-margination and/or thromboses, Ig and/or C4d+

3. Borderline changes - "Suspicious" for acute cellular rejection
   This category is used when no intimal arteritis is present, but there are foci of mild tubulitis (1 to 4 mononuclear cells/tubular cross section) and at least i1

cells/tubular cross section or group of 10 tubular cells)

IB	Cases with significant interstitial infiltration (> 25% of parenchyma affected) and foci of severe tubulitis (> 10 mononuclear cells/tubular cross section or group of 10 tubular cells)
IIA	Cases with mild to moderate intimal arteritis (v1)
IIB	Cases with severe intimal arteritis comprising > 25% of the luminal area (v2)
III	Cases with "transmural" arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)

5. Chronic/sclerosing allograft nephropathy

Grade	Histopathological Findings
Grade I (mild)	Mild interstitial fibrosis and tubular atrophy without (a) or with (b) specific changes suggesting chronic rejection
Grade II (moderate)	Moderate interstitial fibrosis and tubular atrophy (a) or (b)
Grade III (severe)	Severe interstitial fibrosis and tubular atrophy and tubular loss (a) or (b)

6. Other
   Changes not considered to be due to rejection.

Active acute rejection

4. Acute/Active Rejection

Type (Grade)	Histopathological Findings
IA	Cases with significant interstitial infiltration (>25% of parenchyma affected) and foci of moderate tubulitis (> 4 mononuclear cells/tubular cross section or group of 10 tubular cells)
IB	Cases with significant interstitial infiltration (> 25% of parenchyma affected) and foci of severe tubulitis (> 10 mononuclear cells/tubular cross section or group of 10 tubular cells)
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IF/TA

5. ~~Chronic/sclerosing allograft nephropathy~~

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Grade III (severe)	Severe interstitial fibrosis and tubular atrophy and tubular loss (a) or (b)

IB Cases with significant interstitial infiltration (> 25% of parenchyma affected) and foci of severe tubulitis (> 10 mononuclear cells/tubular cross section or group of 10 tubular cells)

5. Interstitial fibrosis and tubular atrophy, no evidence of any specific etiology
(may include nonspecific vascular and glomerular sclerosis, but severity graded by tubulointerstitial features)

Grade

I. Mild interstitial fibrosis and tubular atrophy (<25% of cortical area)

II. Moderate interstitial fibrosis and tubular atrophy (26–50% of cortical area)

III. Severe interstitial fibrosis and tubular atrophy/ loss (>50% of cortical area)

DRAFT PROPOSAL KIDNEY CHRONIC HUMORAL REJECTION

1. Clinical evidence of chronic graft dysfunction
2. Histologic evidence of chronic injury: need 3 of 4
   a. Arterial intimal fibrosis
   b. Duplication of glomerular basement membrane
   c. Interstitial Fibrosis / Tubular Atrophy (IF/TA)
   d. Laminated PTC basement membrane
3. Evidence for Ab action / Deposition in Tissue
   - C4d in PTC
4. Serologic evidence of anti-HLA antibody

AST/ASTS Conference on Humoral Rejection. Bethesda, April 2003

Chronic active T-cell mediated rejection

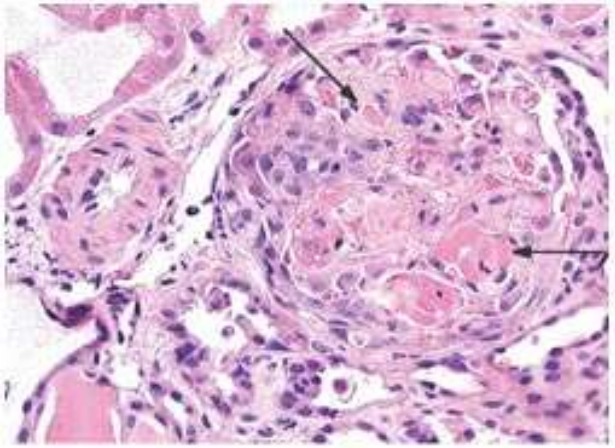
Graft Chronic Arteriopathy:

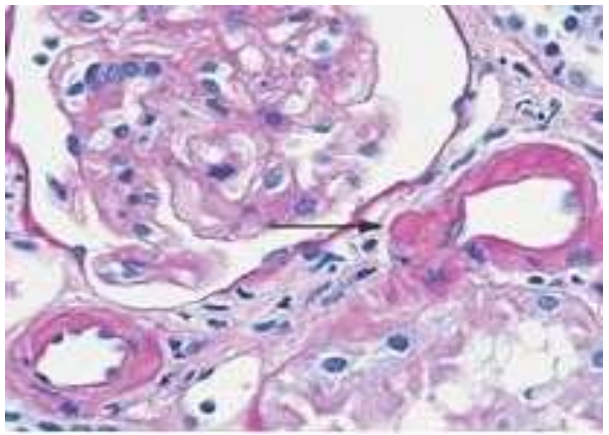
1. Arterial intimal fibrosis with lymphomononuclear cellular infiltration and fibrosis.

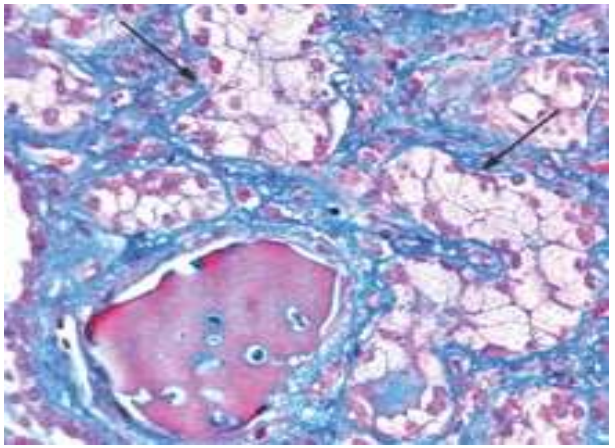
2. Development of a neointima

Drug toxicity: Changes

1. Due to calcineurin inhibitors:
   - Thrombotic microangiopathy
   - Hialine arteriolosclerosis
   - Isometric tubular vacuolization
2. Tubulo-interstitial nephritis







Infection

1. **Bacterial:**

   Acute or chronic pyelonephritis

2. **Other agents:**

   A. Viral:

   - *Cytomegalovirus*

   - *Adenovirus*

   - *Polyomavirus*

   B. Fungal:

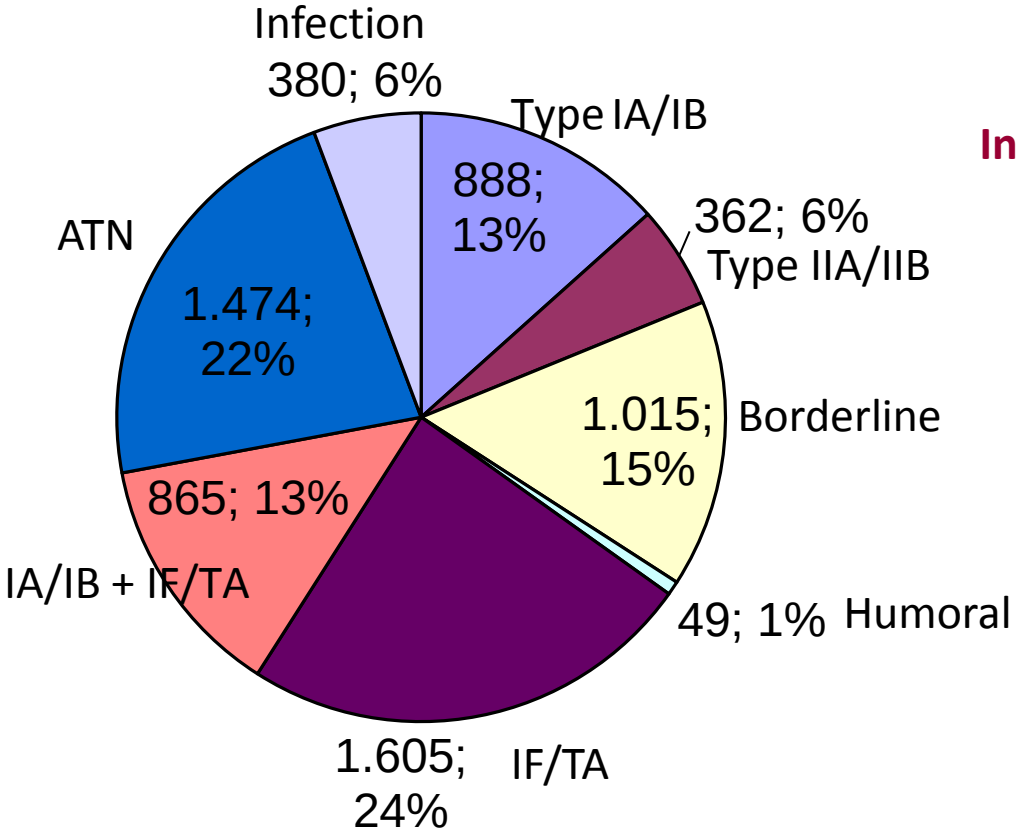
   - ***Mucormycosis***

   - ***Candida sp***

TX RENAL BXs (2008 - 2010)
Total number of renal bxs: 15100

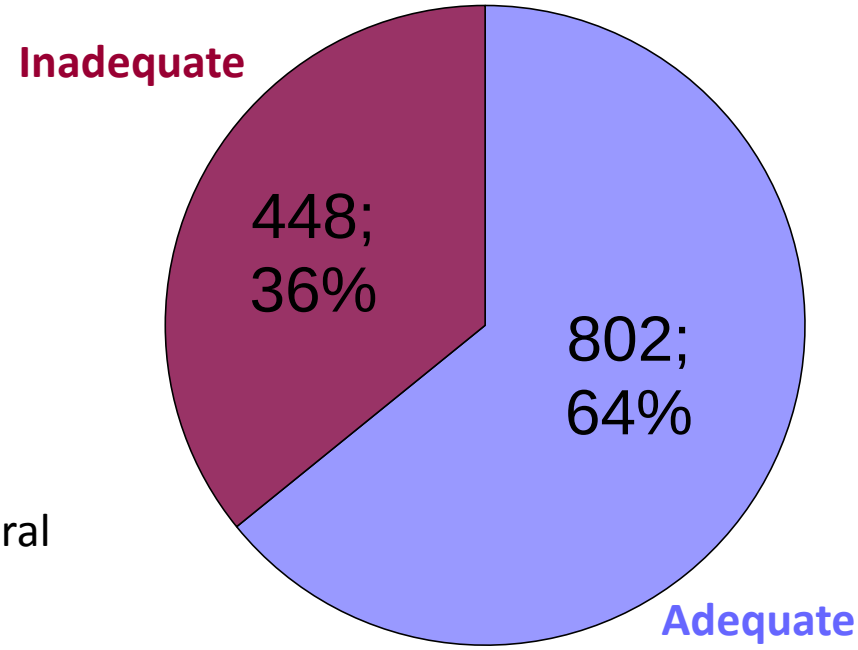
Renal Graft Biopsies 2008-2010

N= 6638



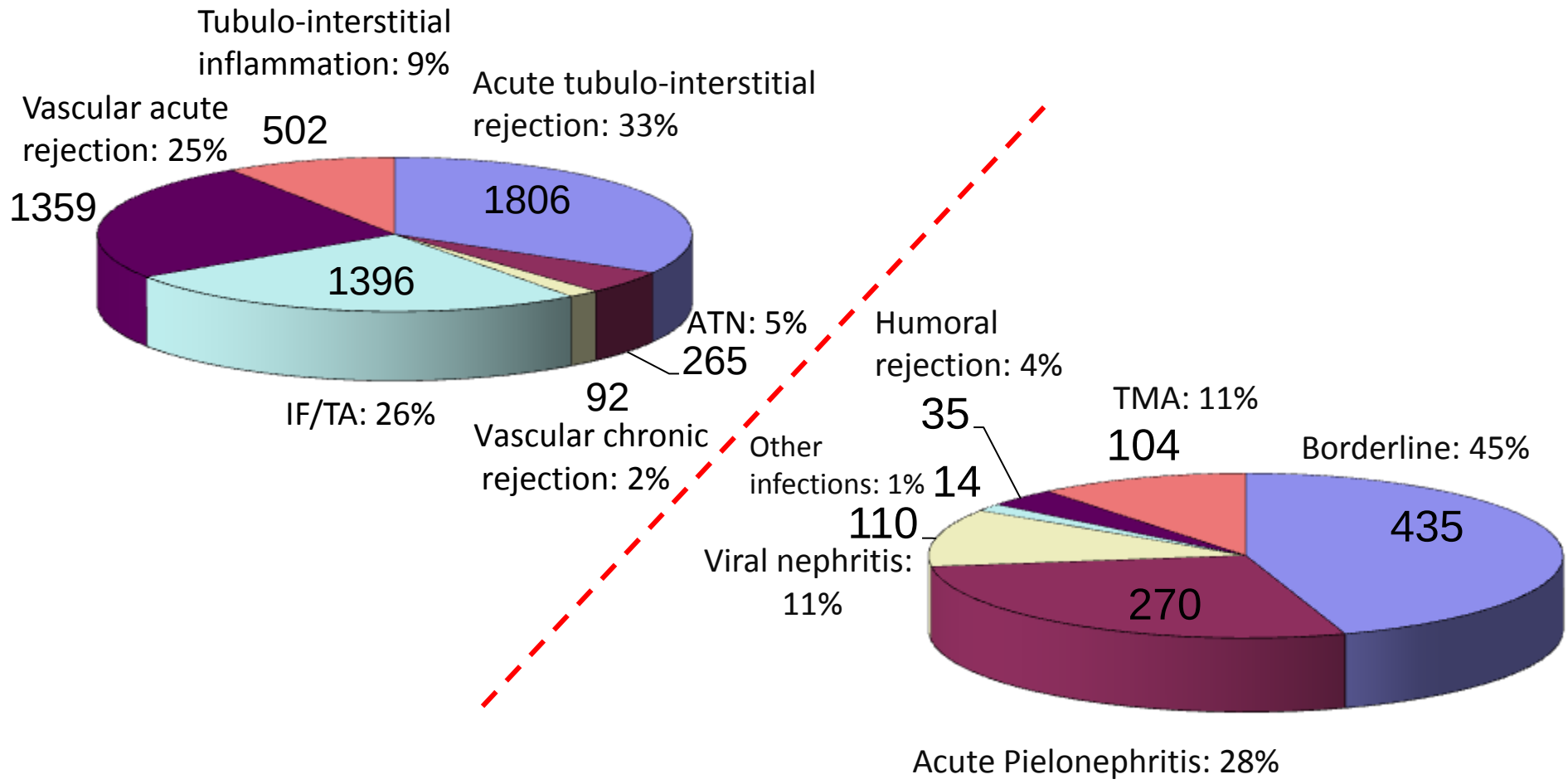
Pre implant donor biopsies

N= 1250



Renal TX-biopsies: 2009 – 2011 period

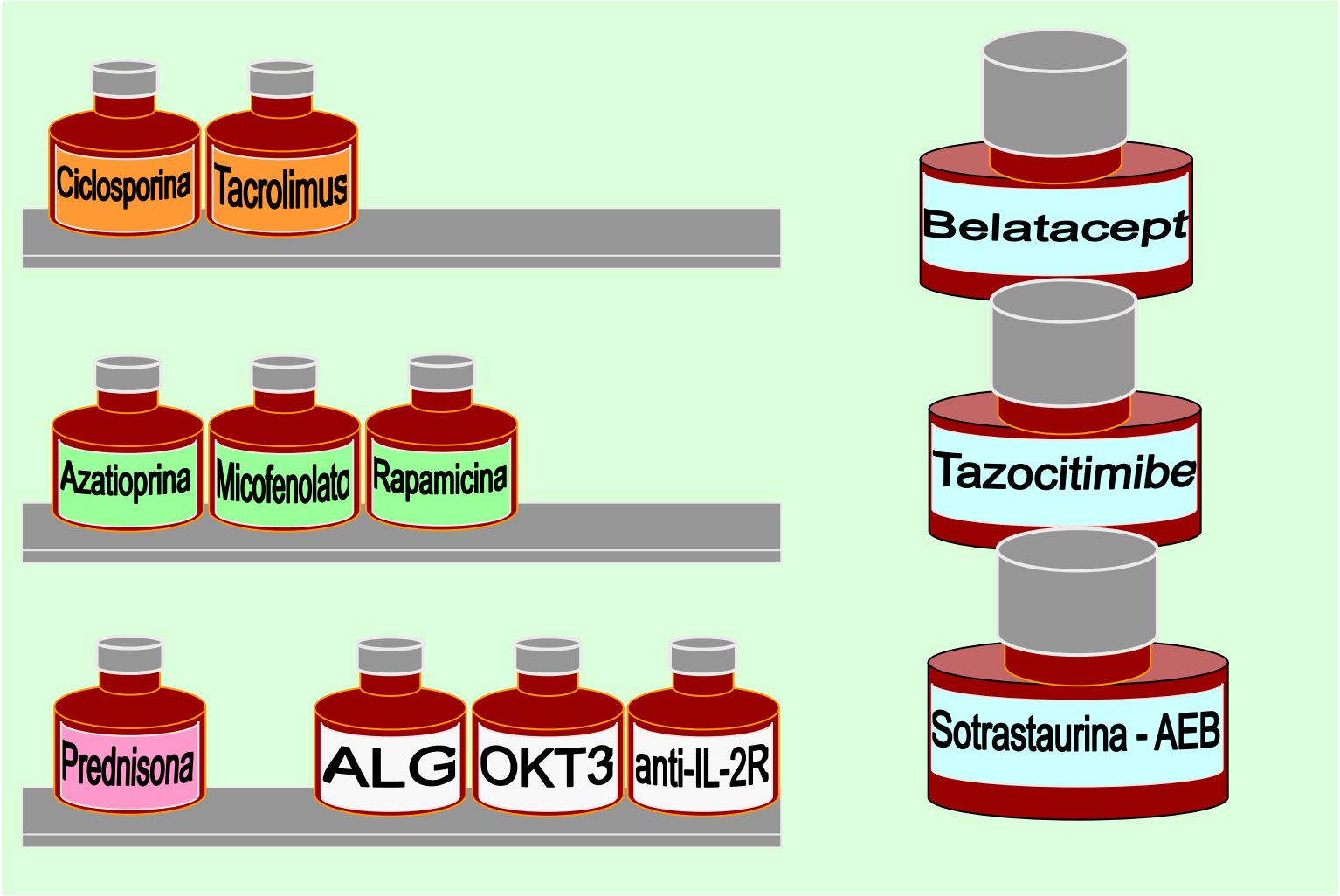
TOTAL NUMBER OF RENAL BIOPSIES: **5420**



Positive aspects of the Brazilian programme

- Universal access to the Public Health Service (SUS)
- National Tx System well organized and structured
- Permanent free access to the immunossupressive drugs
- Brazilian people are more and more conscious of the importance of organ donation
- Organs for cadaveric donors are to be used exclusively for the local native population
- Committees in all hospitals for dealing with Tx affairs (CIHDOT)

IMMUNOSSUPPRESSIVE DRUGS AVAILABLE FOR FREE (SUS)

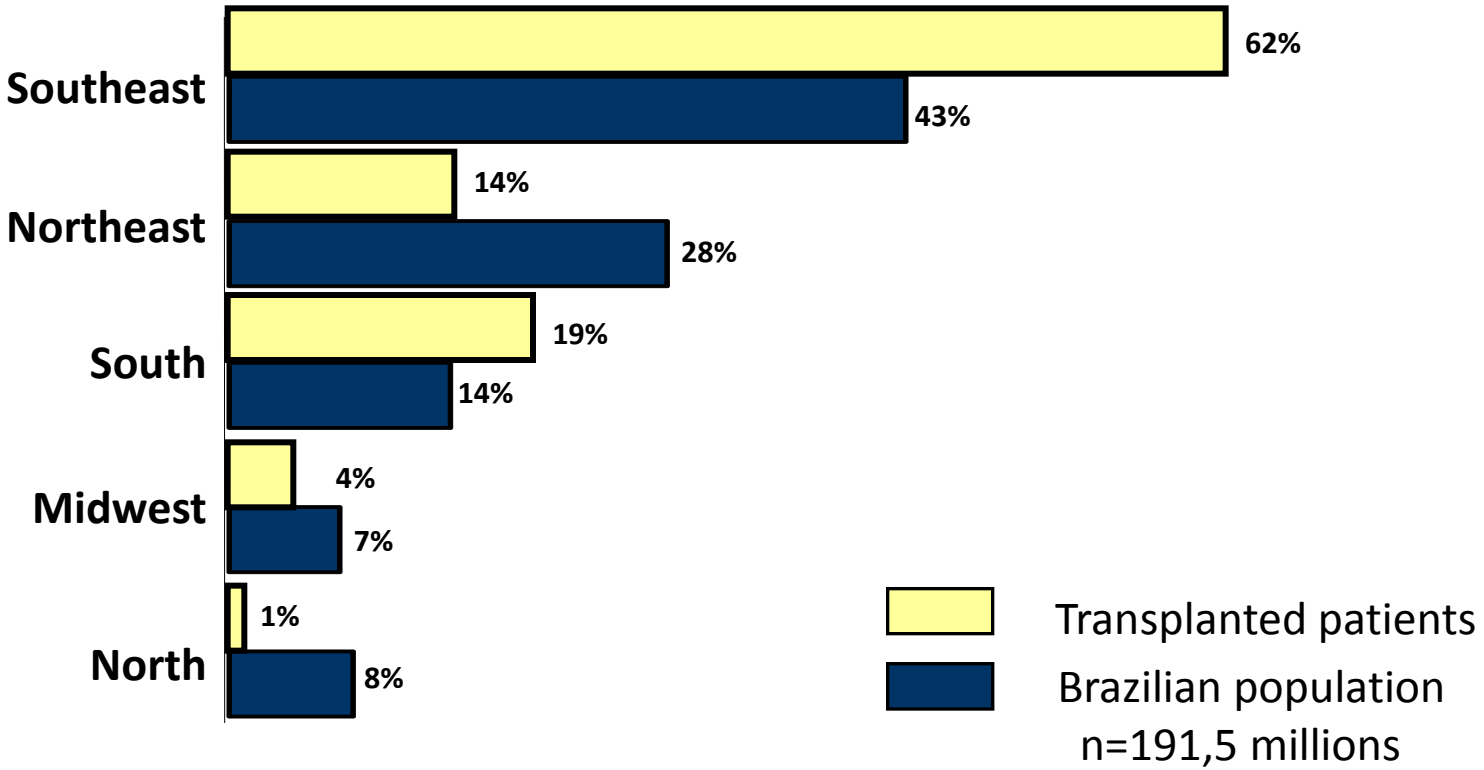


How to double the number of renal Tx??

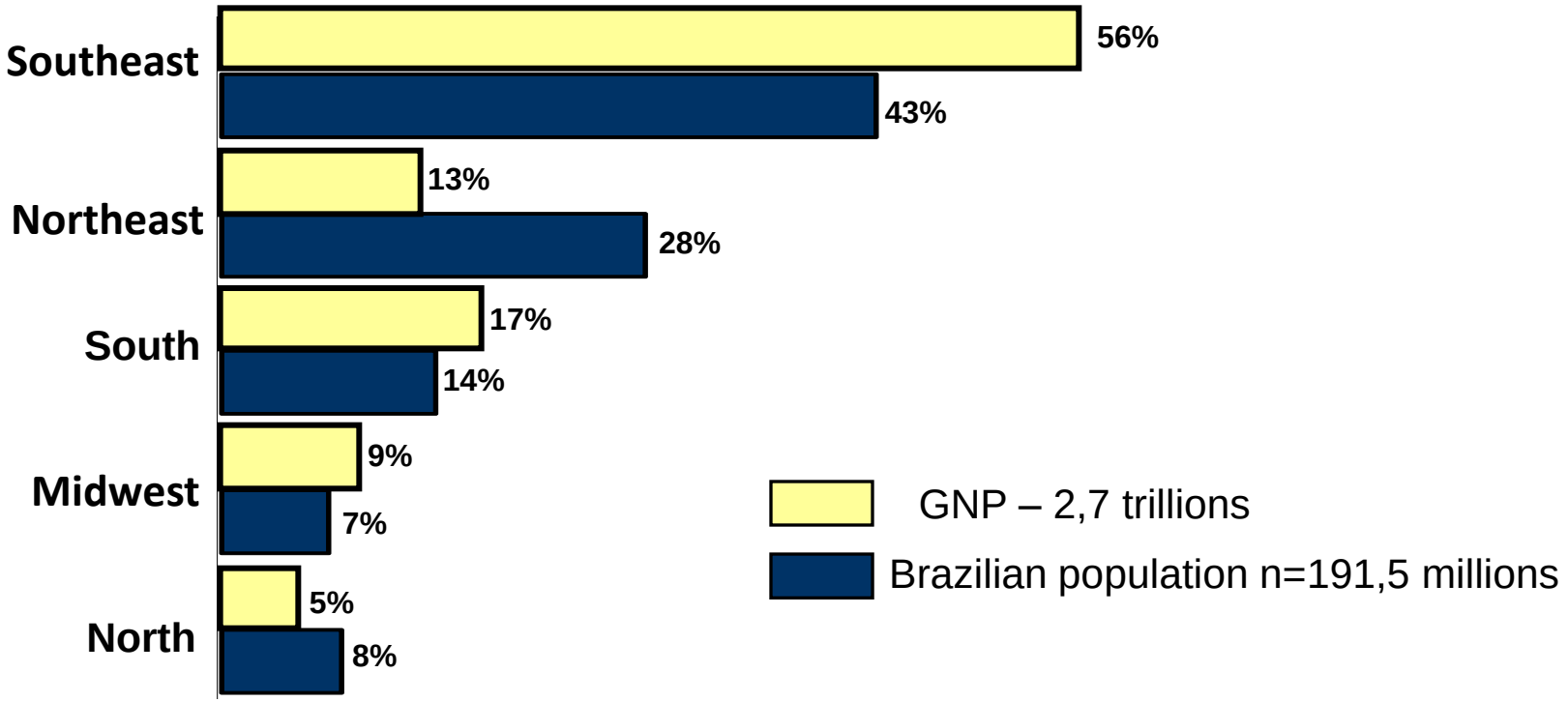
- To reduce the geographic disparity
- To increase the number of medical staff in the Tx programme
- Campaign for early notifitication of potential donors
- To use donors after heart acute failure
- To establish criteria to accept kidneys with expanded criteria
- Preemptive Tx: to locate potential living donors for patients in the waiting list
- Campaign to increase the survival of renal graft in the black population
- To better define when renal Tx is more suitable than dialysis

Brazilian regions

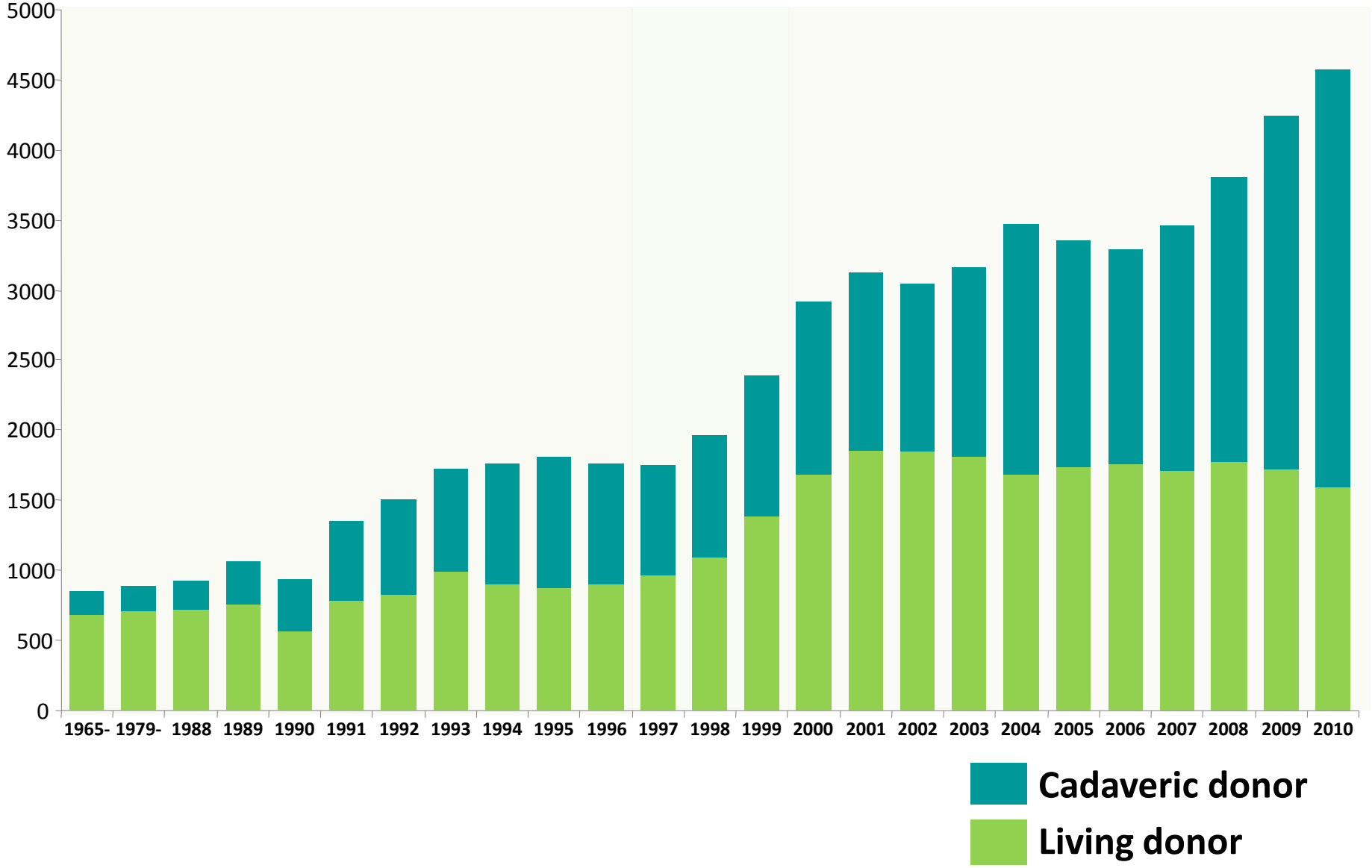
REGIONAL DISTRIBUTION OF THE NUMBER OF RENAL TX IN BRAZIL



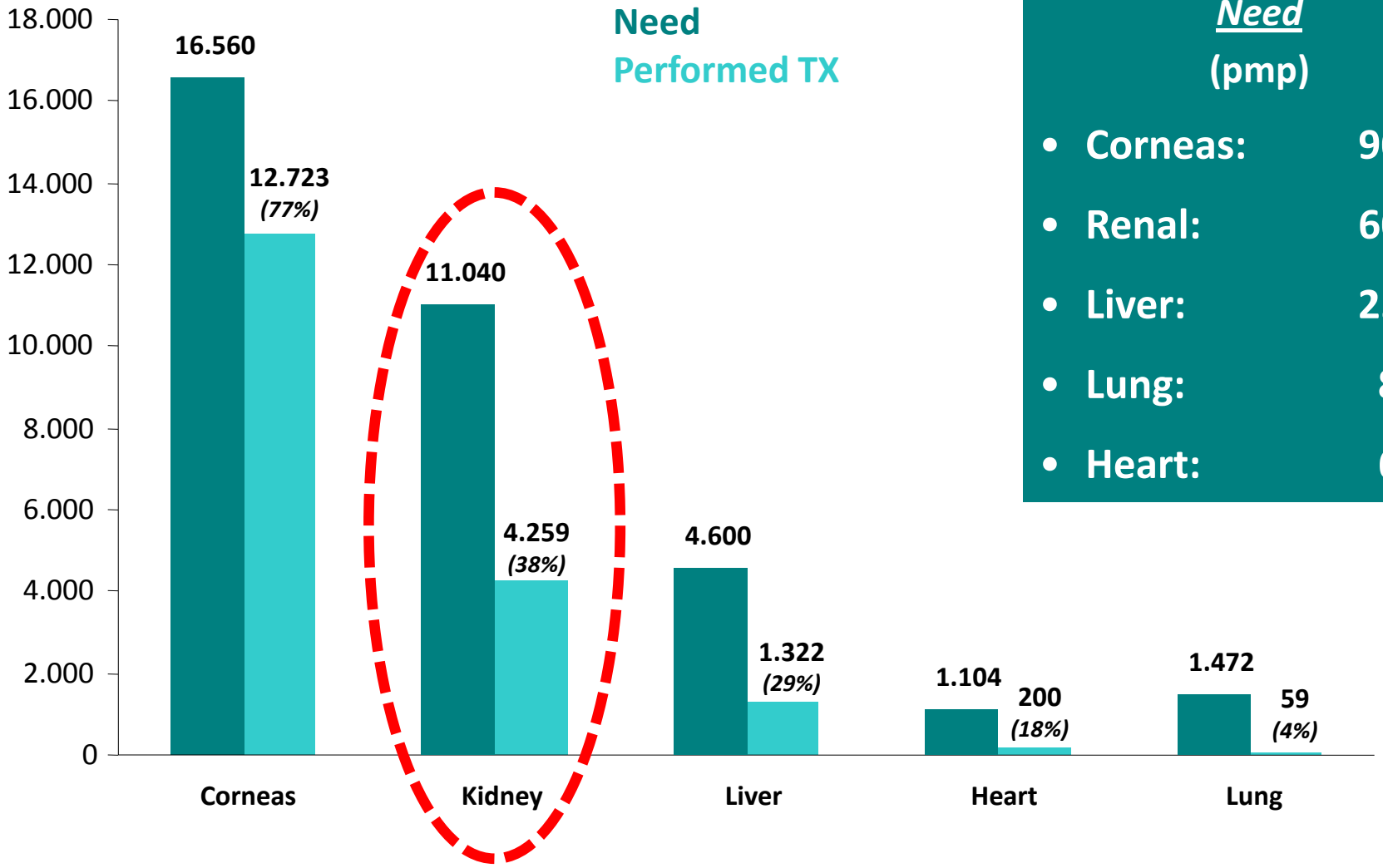
REGIONAL BRAZILIAN POPULATION /REGIONAL BRAZILIAN GNP



ANNUAL NUMBER OF KIDNEY TRANSPLANTS PERFORMED IN BRAZIL

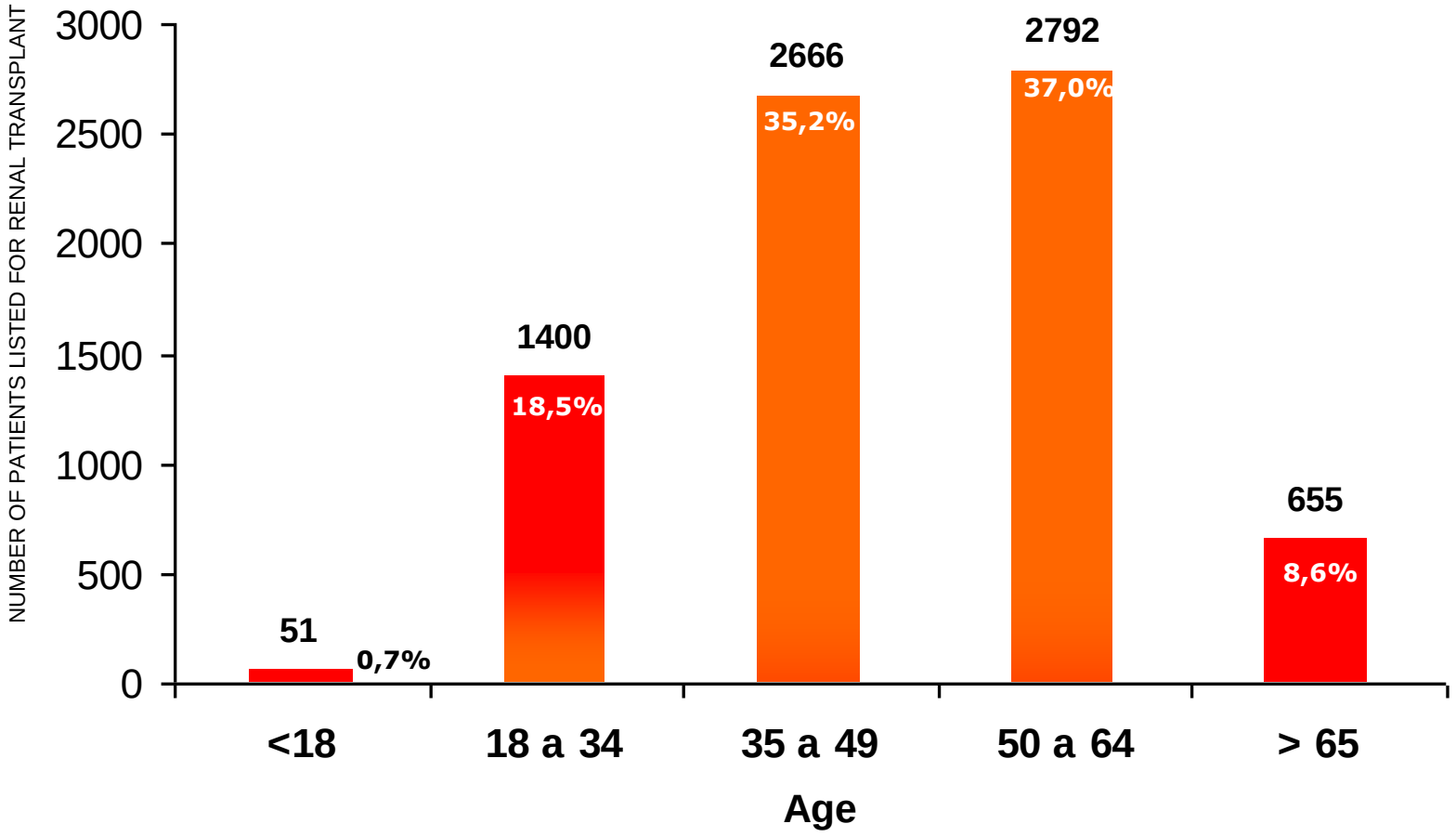


ESTIMATED NEED VS. PERFORMED TRANSPLANTS IN 2010

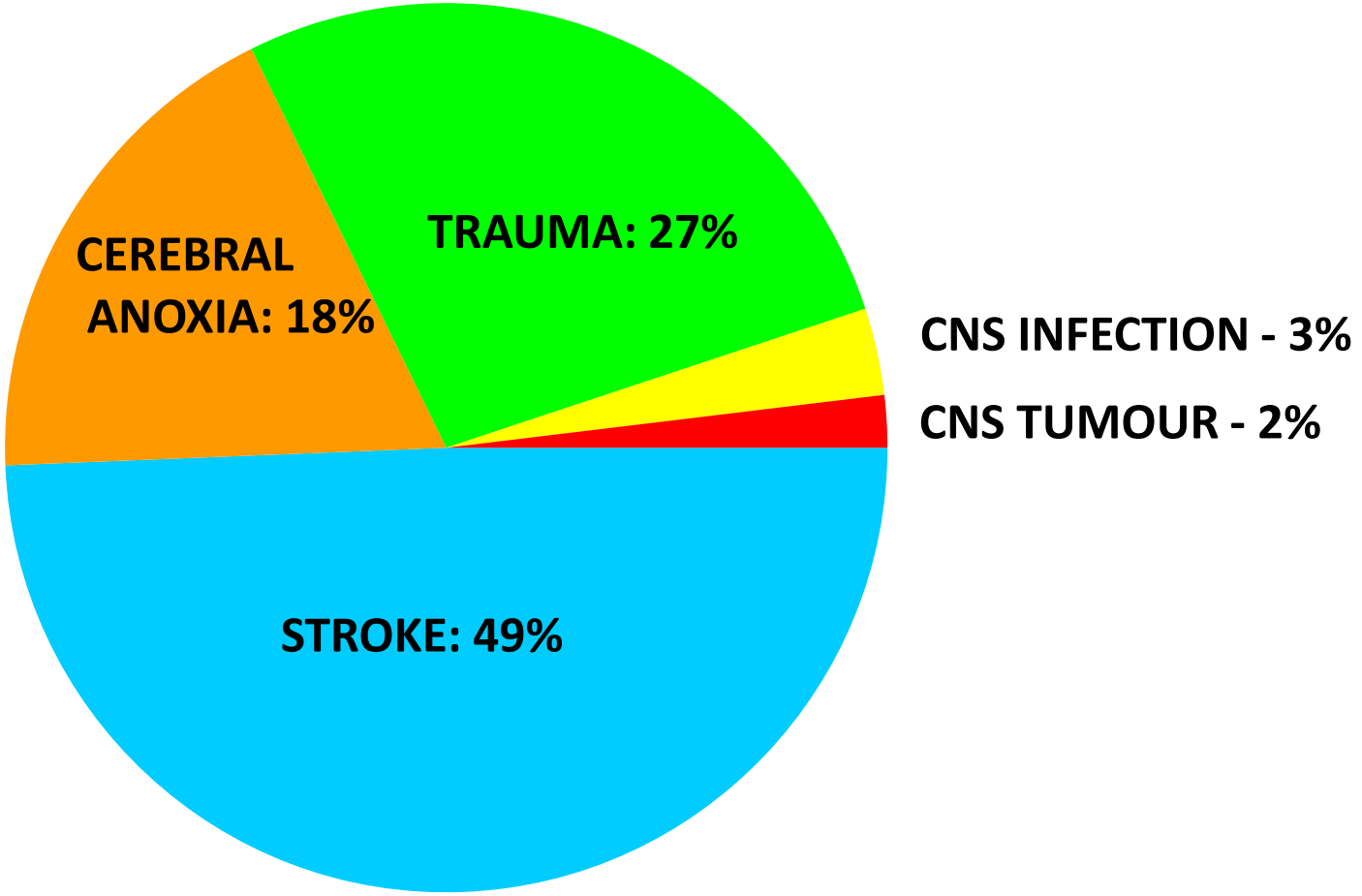


Need (pmp)	
• Corneas:	90
• Renal:	60
• Liver:	25
• Lung:	8
• Heart:	6

AGE RANGE FOR THE 7564 PATIENTS LISTED FOR RENAL TRANSPLANT IN THE STATE OF SAO PAULO



CAUSE OF DEATH OF THE DONORS UNIFESP-EPM IN 2010



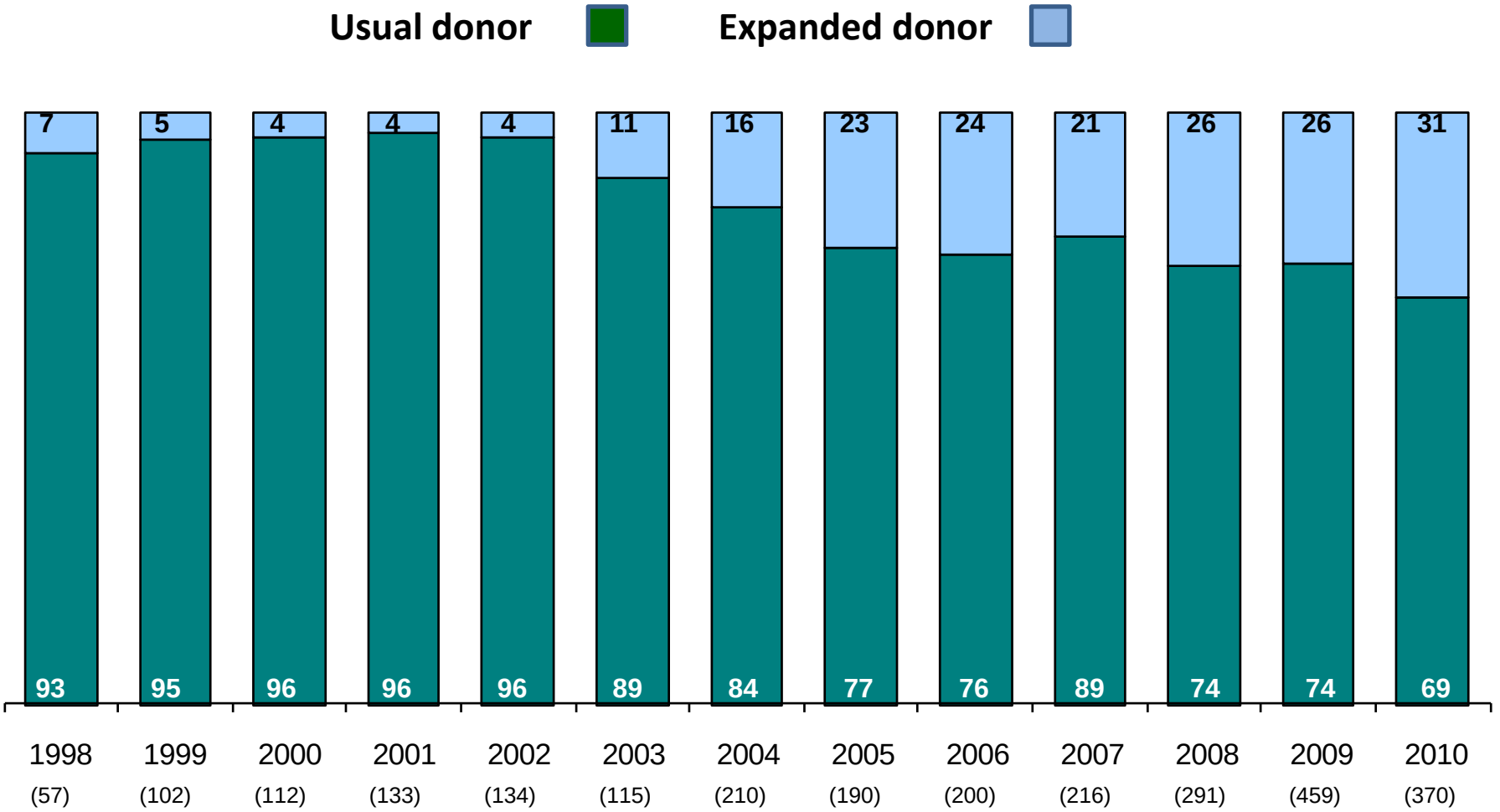
INCREASE IN THE NUMBER OF DONORS WITH EXPANDED CRITERIA

- Age > 60 anos

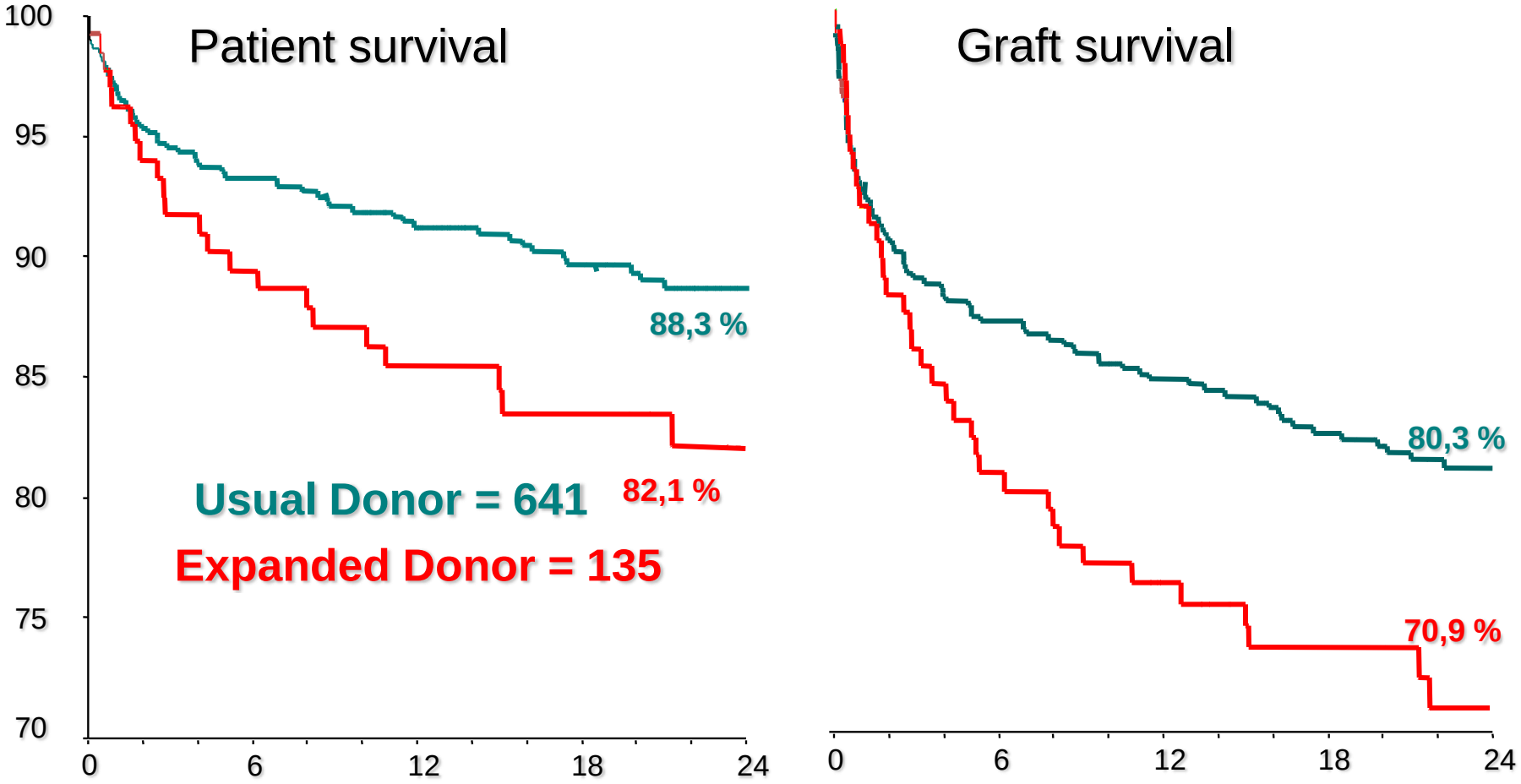
- Age > 50
  - Arterial hypertension
  - Creatinine > 1.5 mg/dL
  - Stroke = Cause of death

§Relative risk of graft loss > 1.7

ANNUAL PROPORTION OF RENAL TRANSPLANT WITH EXPANDED CRITERIA DONOR (KIDNEY AND HYPERTENSION HOSPITAL)

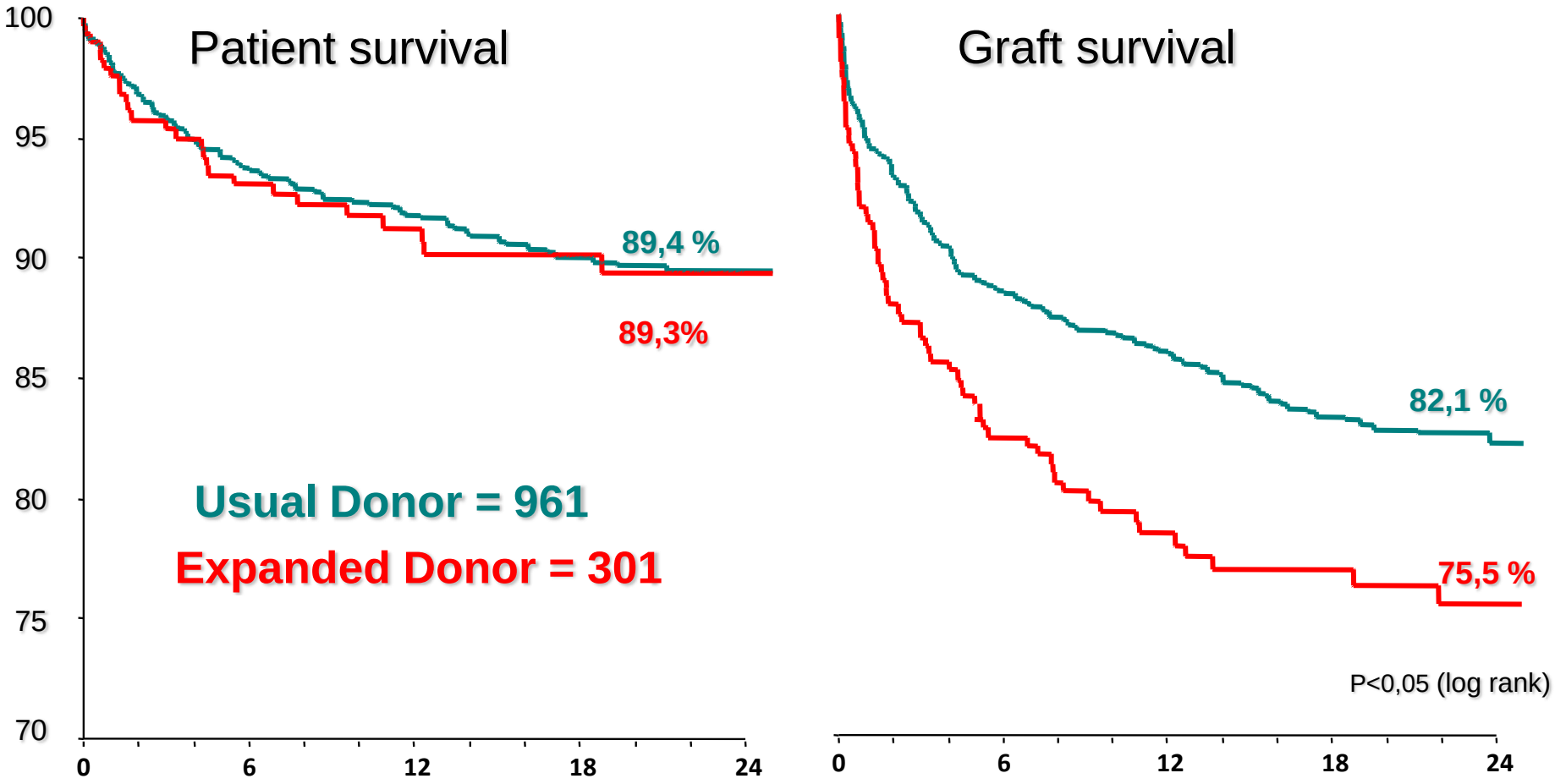


SURVIVAL OF DECEASED DONOR TRANSPLANTS (2003 - 2006) UNIFESP

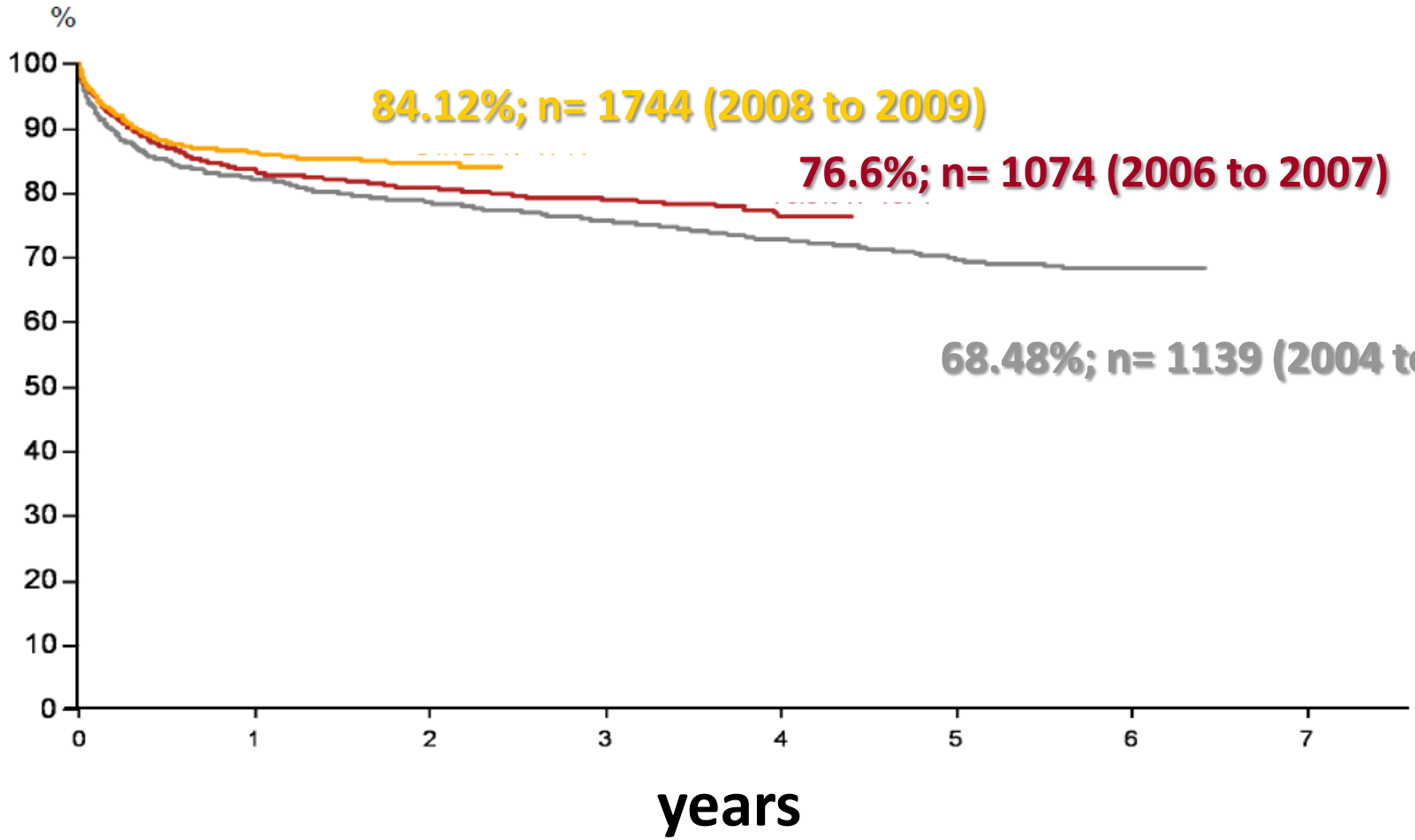


P<0,05 (log rank)

SURVIVAL OF DECEASED DONOR TRANSPLANTS (2006 - 2009) UNIFESP



Survival of the graft for period of years



Cadaveric donor biopsy – "Pre - implant"
Marginal donors

- **Glomerulosclerosis (controversial subject)**
  - **< 20% of the glomeruli:**
    - **Low incidency of DGF: (33% vs 87%)**
    - **Graft loss: 7% vs 38%**
- **Aterosclerosis**
  - **Increase in 6% of graft loss after 2 years**
- **Interstitial fibrosis**
  - **>40% of the cortical extension**
- **Thrombotic MA (3%-7% of the bxs.)**
  - **DGF → no change of graft survival after 2 years**

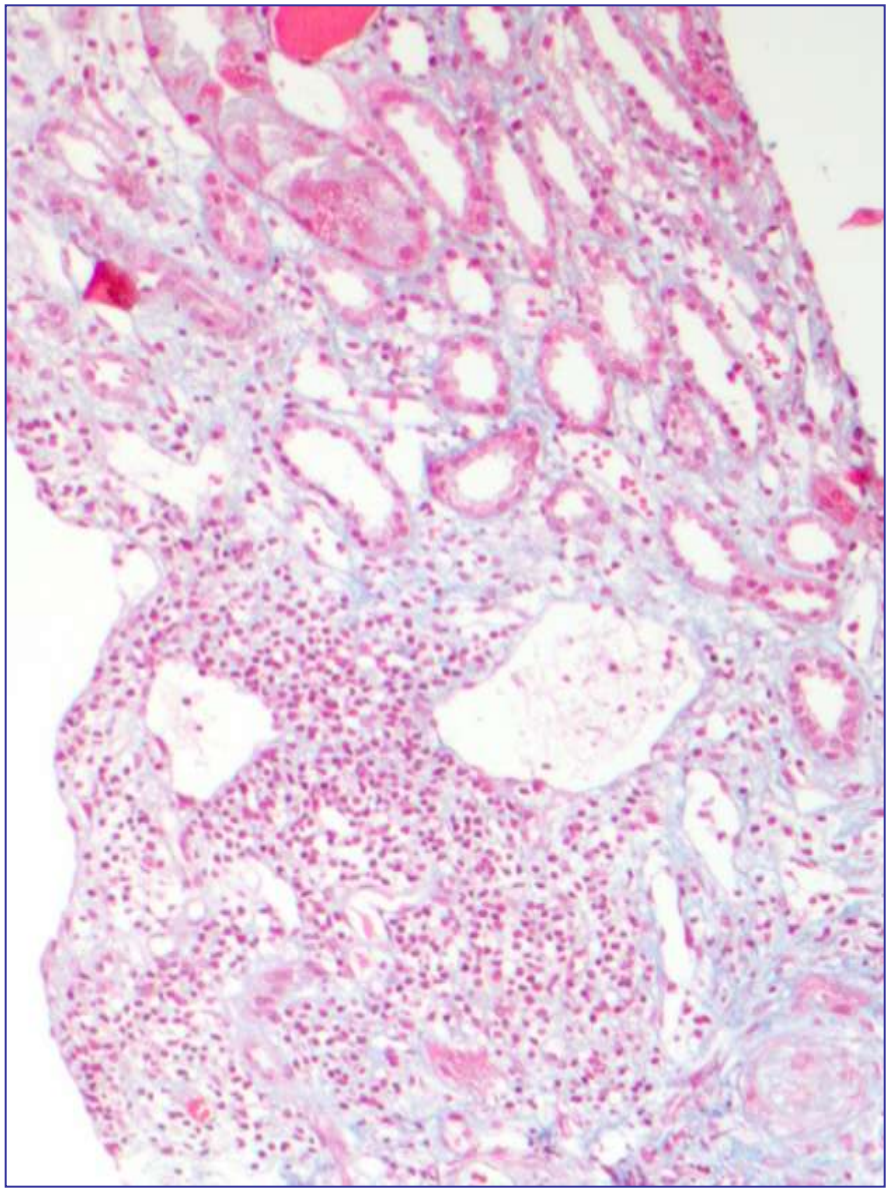
(Heptinstall's, 6th ed. 2007)

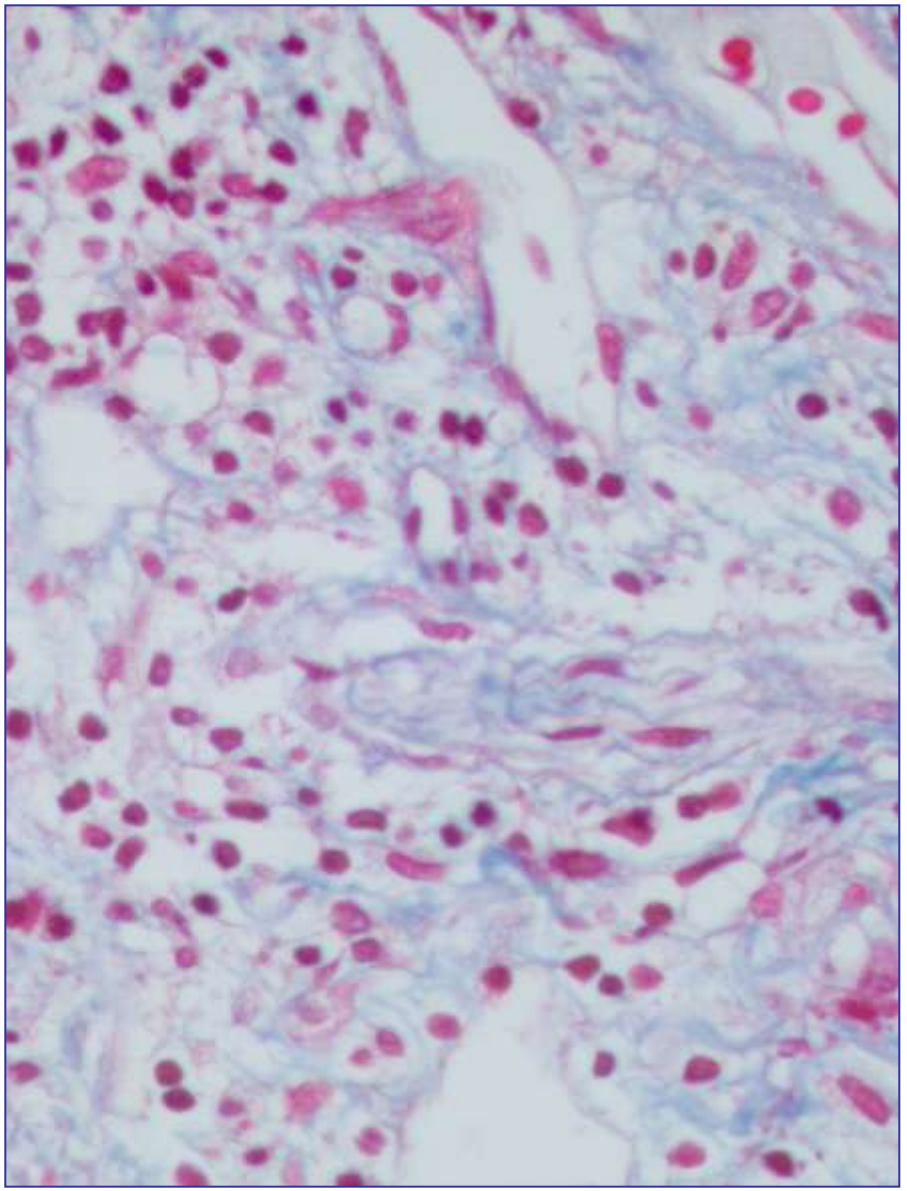
Main diagnostic difficulties:

1. Interstitial inflammation in medulla
2. Inflammation in scar areas-Chronic rejection
3. Subclinical rejection/ Protocol biopsy
4. Samples with different histology
5. Infection associated with Acute rejection ?
6. Intimitis and Donor atherosclerosis
7. Focal and Segmental Glomerulosclerosis in Tx bxs
8. Treated ACRejection-Residual or Persistent inflammation?
9. Special stains next day & No sample left in the paraffin block

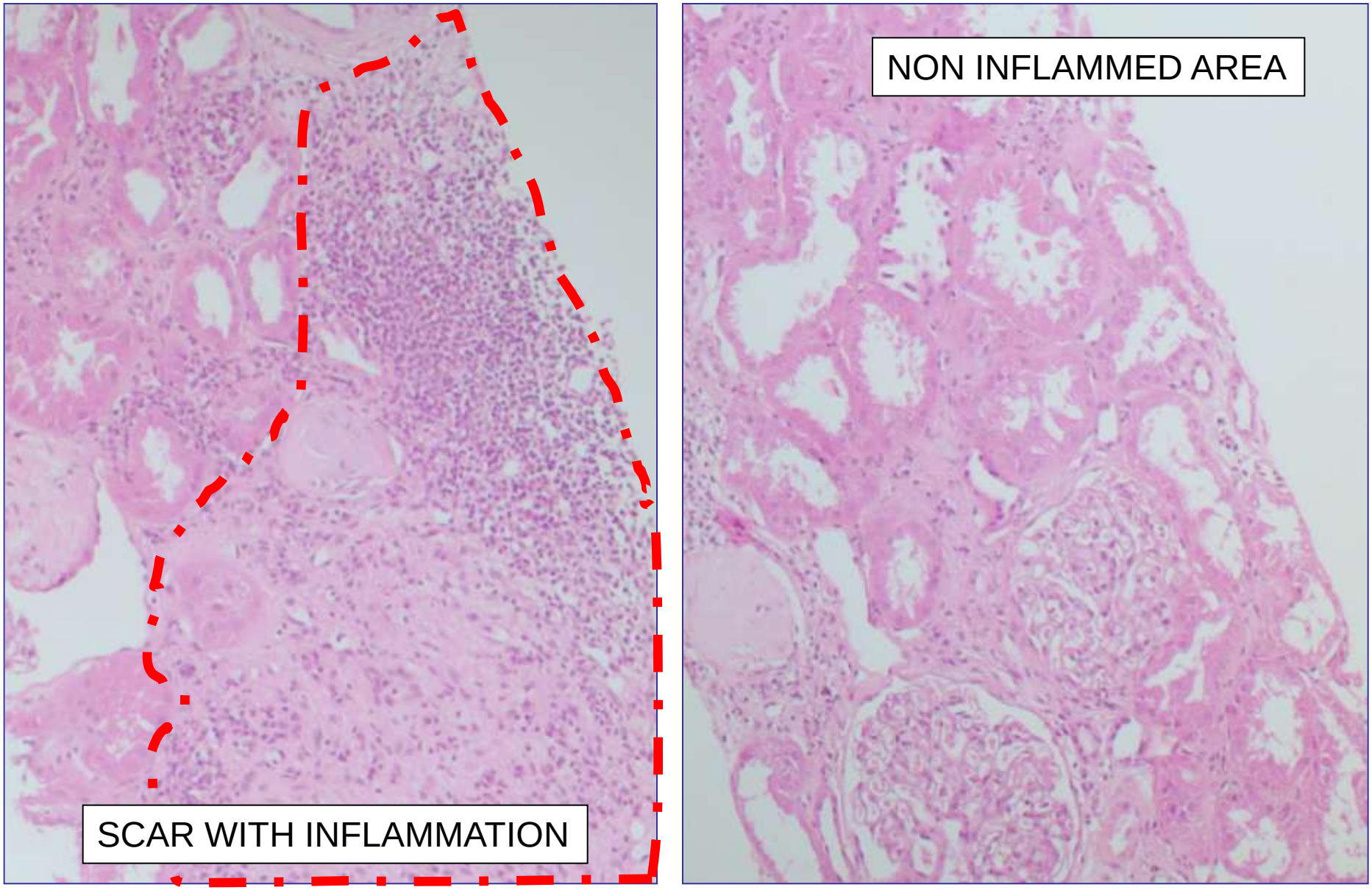
1. Interstitial inflammation in medulla

Acute cellular rejection in medulla





2. Chronic Rejection

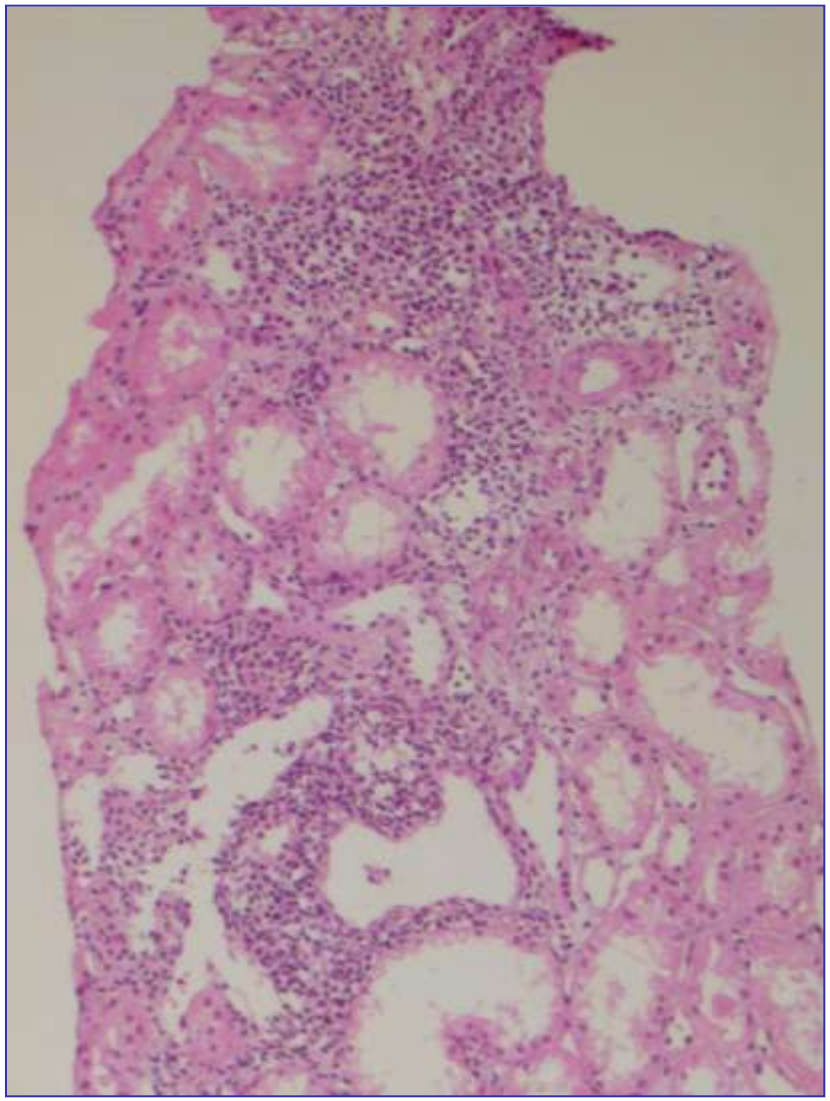


3. Subclinical Rejection

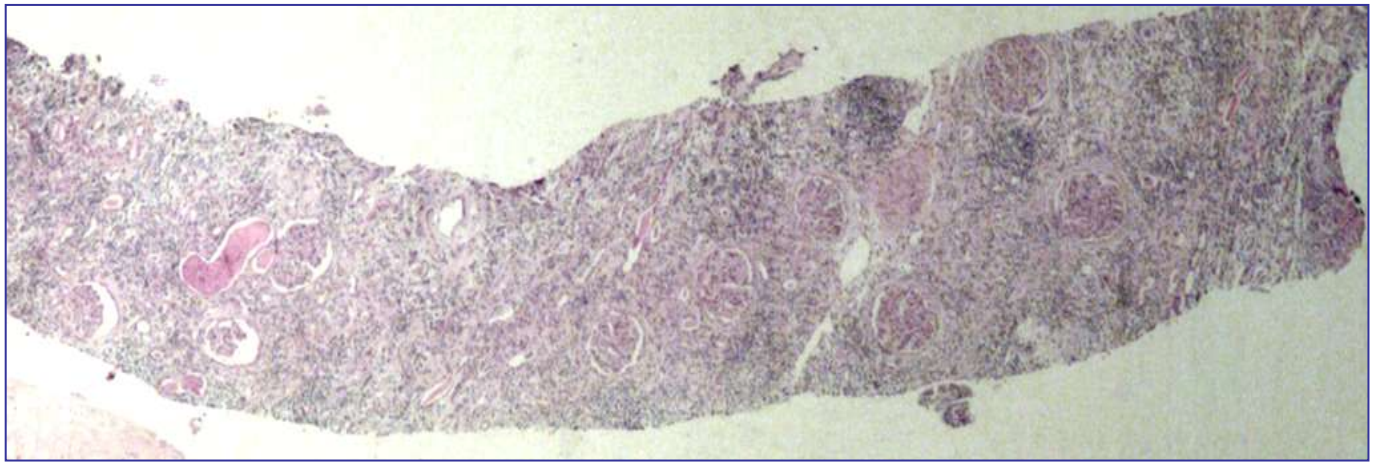
What does it mean for the patient?

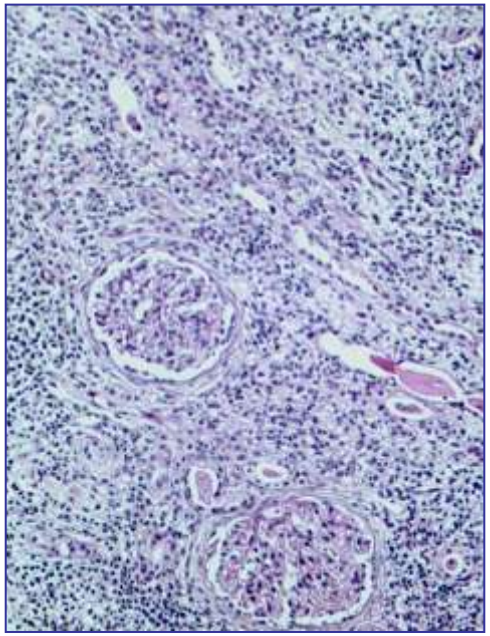
1. Nobody knows for sure.
2. Not to place any diagnostic value on this observation.
3. If the infiltrate is VIVID with interstitial edema, HLA-DR expression may help in diagnosing acute rejection.

(Nickeleit V. by e-mail, 2010)

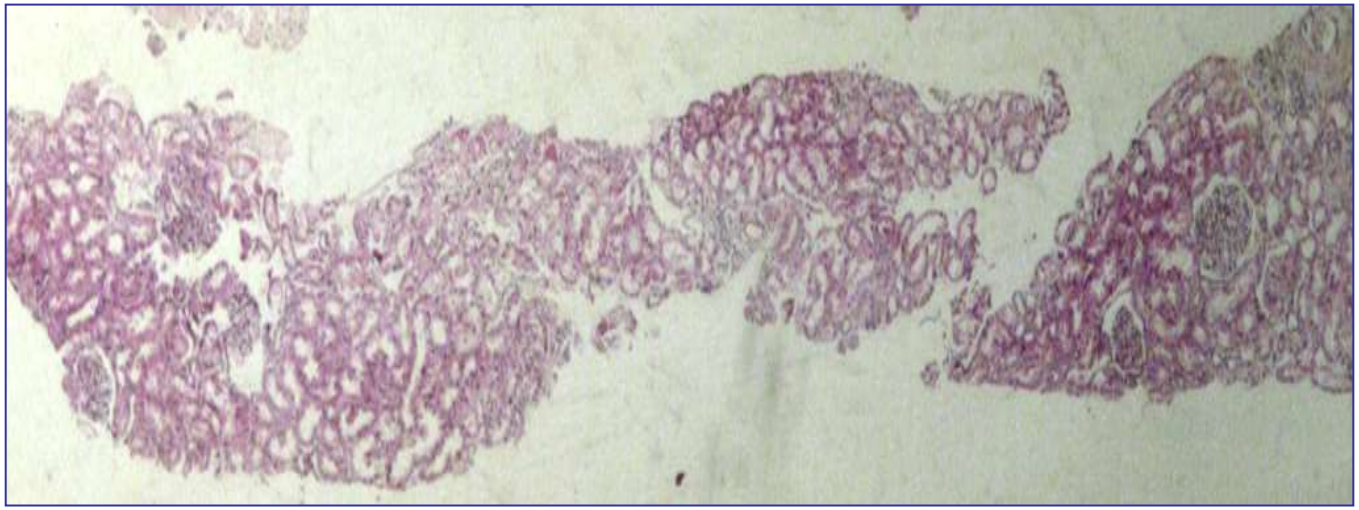


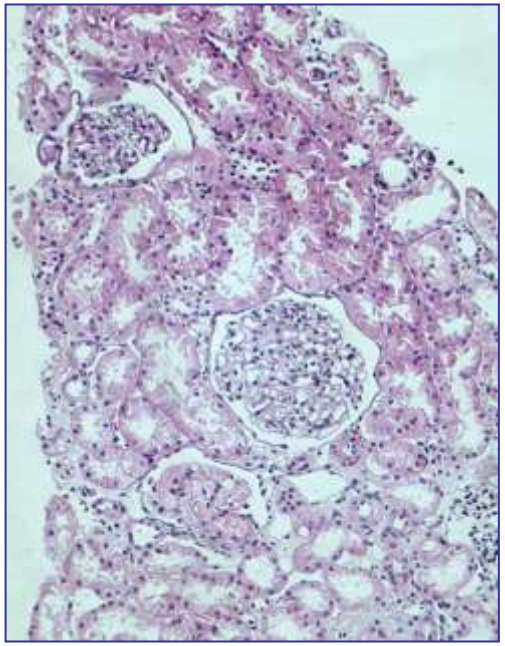
4. Sample problem ???



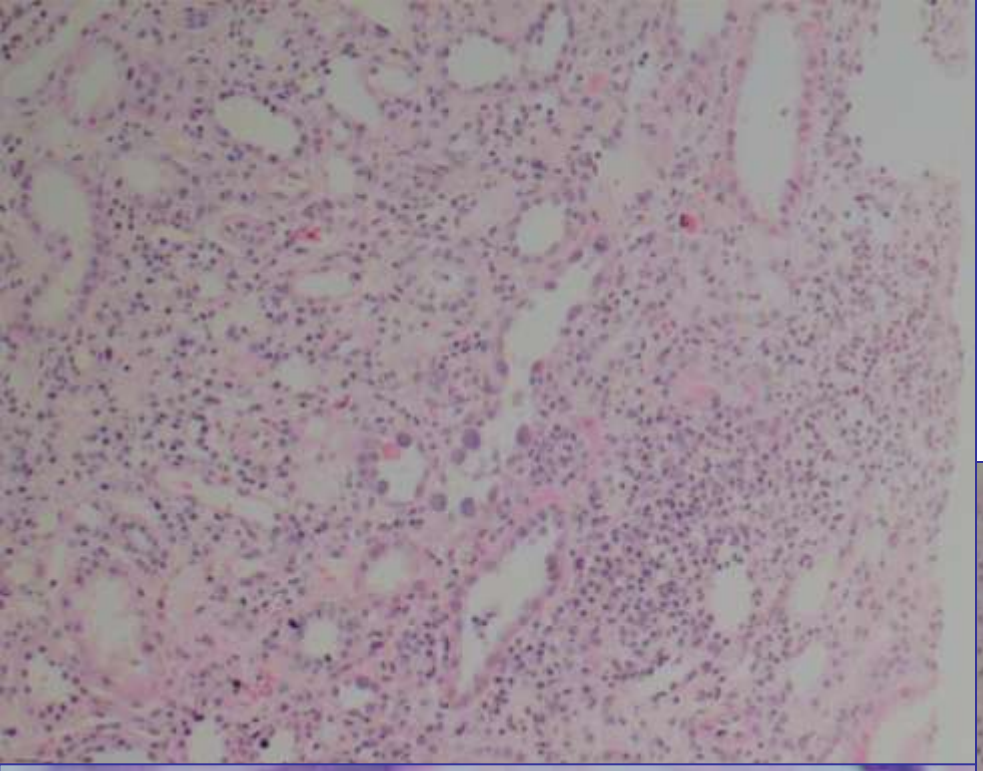


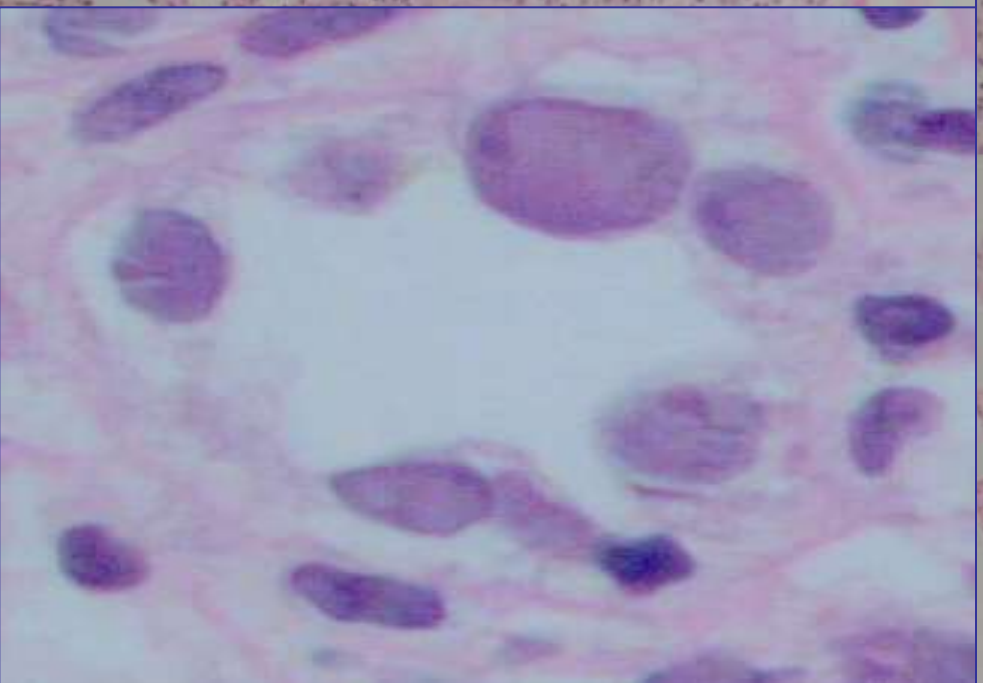
Two cores with totally distinct features

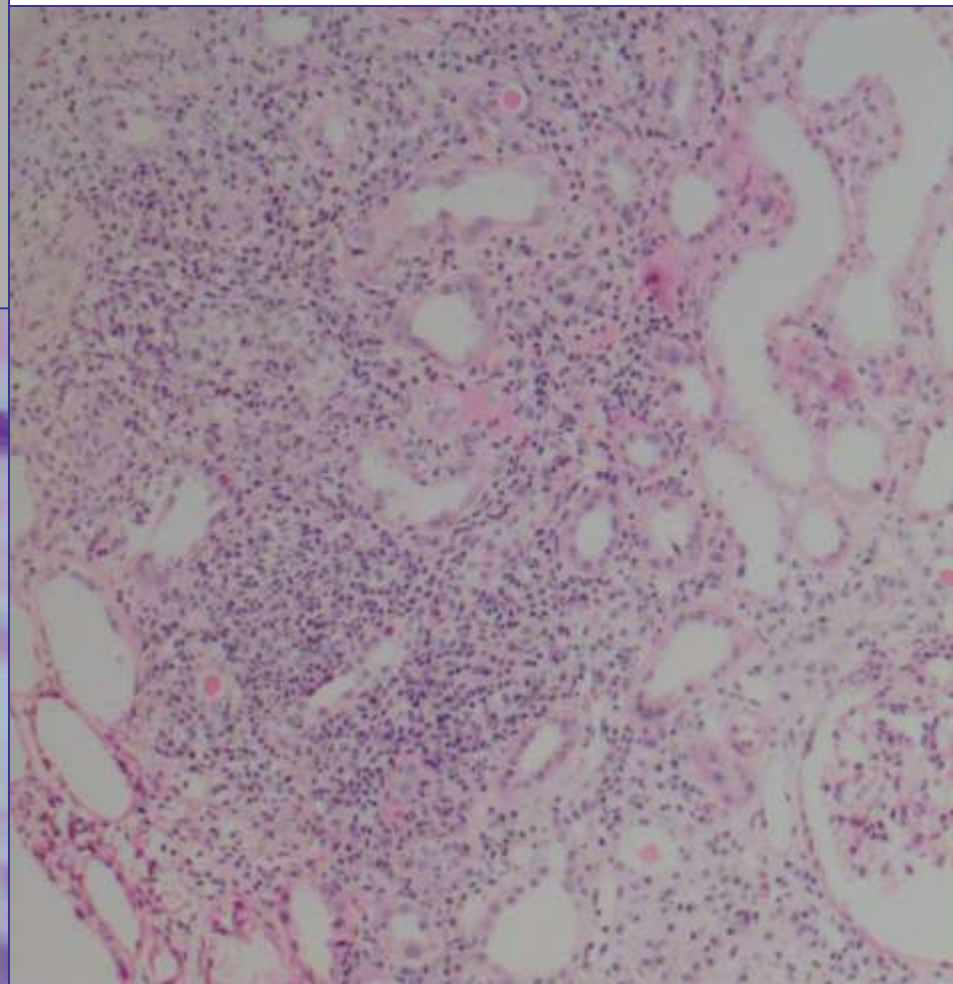




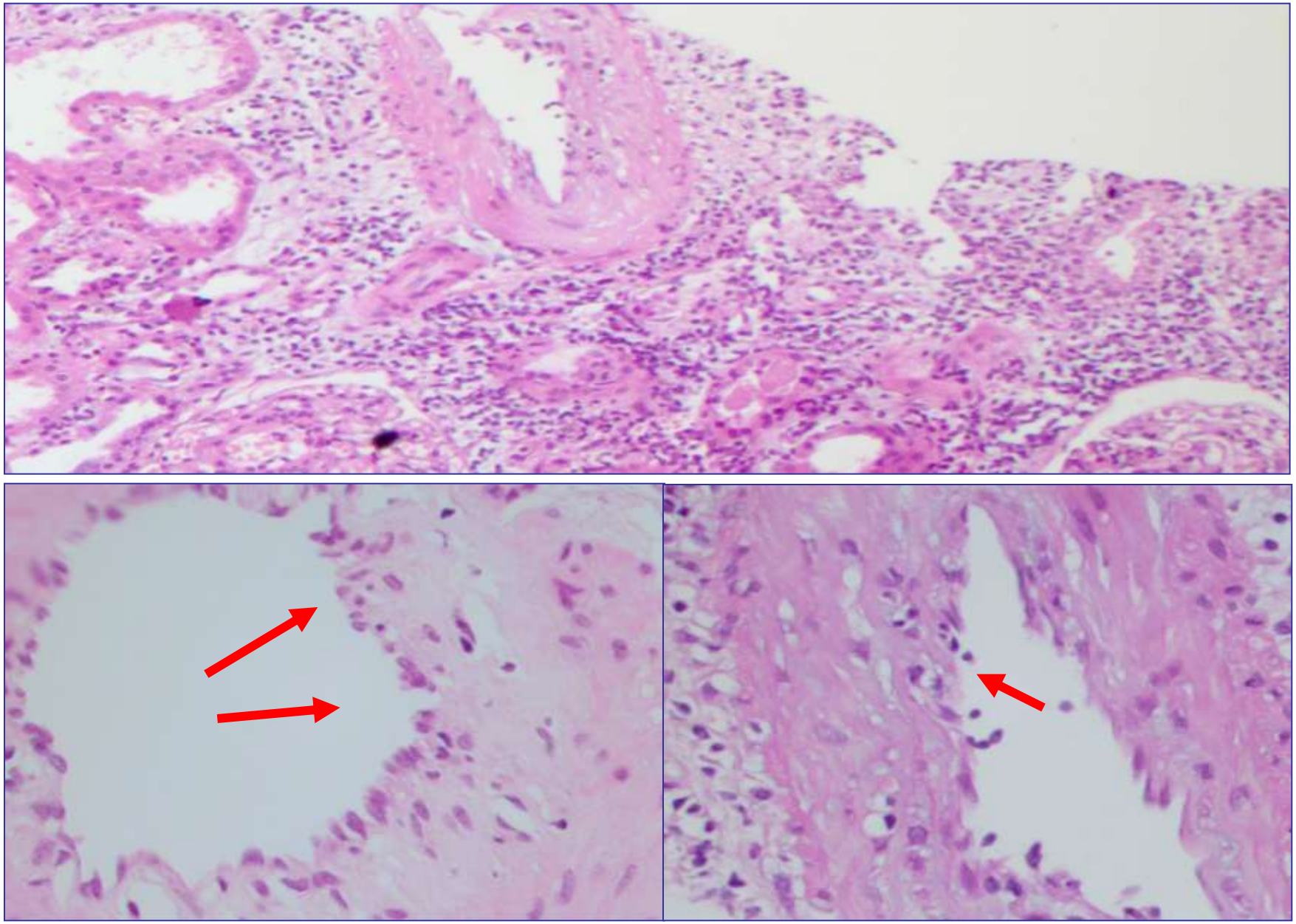
5 - BK NEPHRITIS ASSOCIATED WITH ACUTE CELLULAR REJECTION ??





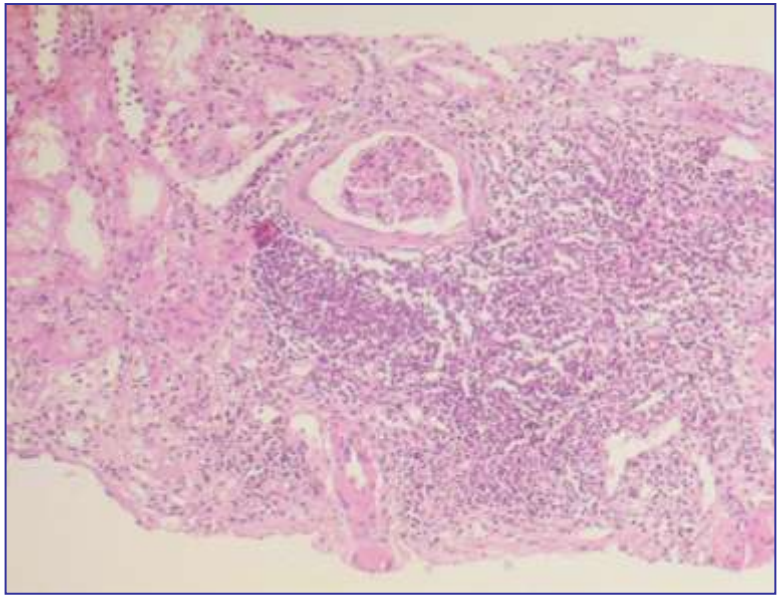


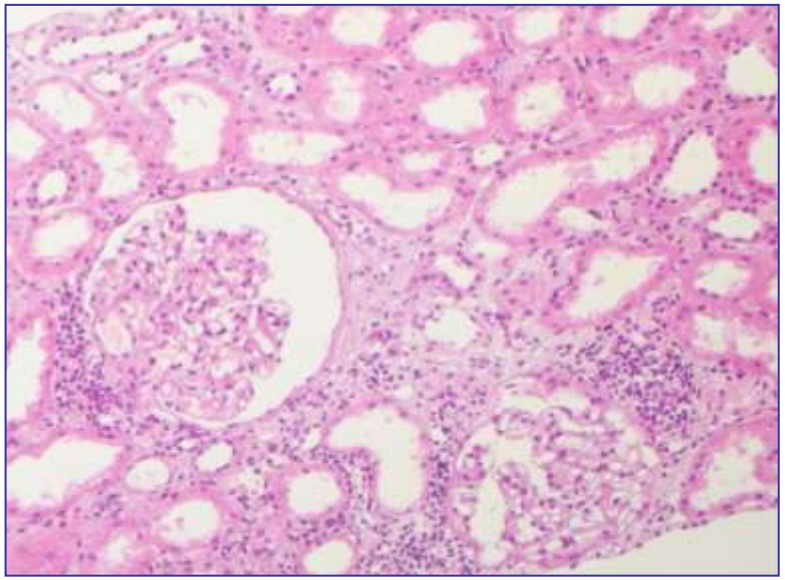
6 - Arteriosclerosis + intimitis????



8 - TREATED ACR: RESIDUAL OR PERSISTENT INFLAMMATION?

- Common bxs to control the efficacy of the treatment.
- Has the treatment abrogate the acute cellular rejection episode?
- When to use the words: Persistent versus Residual, insignificant non-active inflammation ??





9 - Daily difficulties

1. Too many bxs daily plus 3 weekly clinico-pathological meetings. **(3 Nephropathologists)**
2. In addition, there are the bxs of native kidneys.
3. The special stains due to the great daily routine are only available in the next morning. They may show important additional features not presented in the original HE microslide.
4. Very little material left in the paraffin blocks, which becomes a problem for further IHC or genetic studies.


OBRIGADO
GRACIAS
THANKS