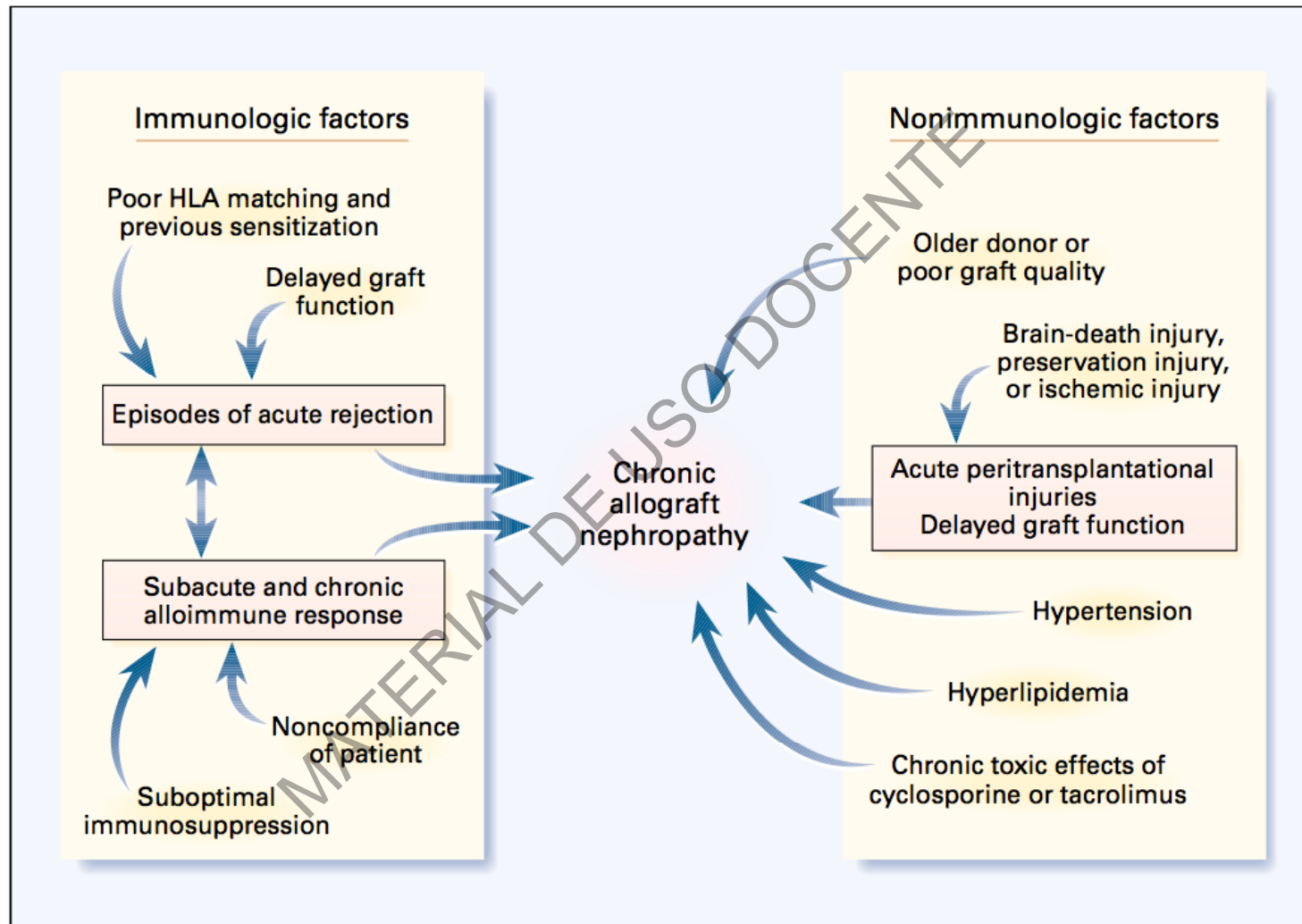


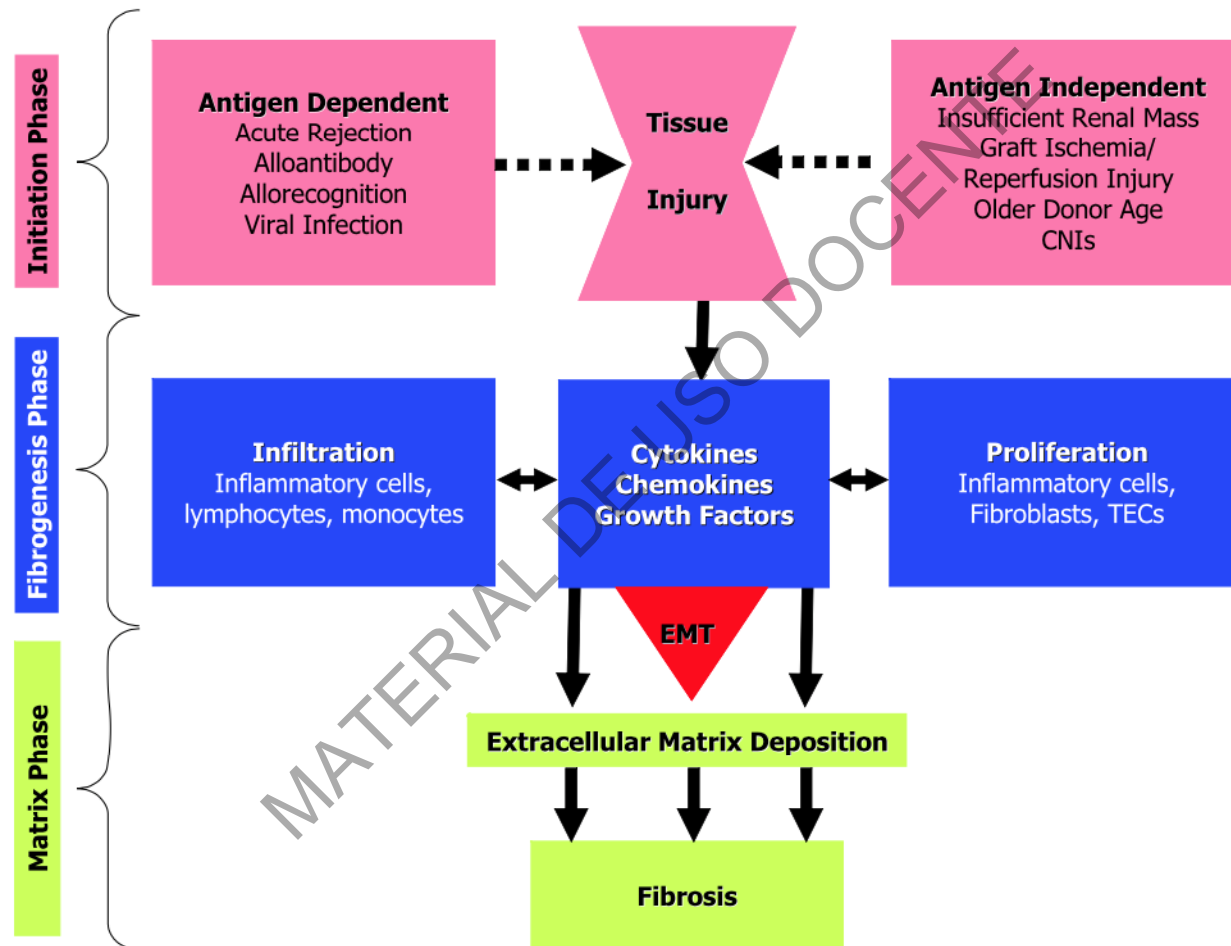
Rechazo crónico mediado por anticuerpos. Tratamiento y pronóstico

Federico Oppenheimer
Servicio de Nefrología y Trasplante Renal
Hospital Clínic de Barcelona
oppen@clinic.ub.es

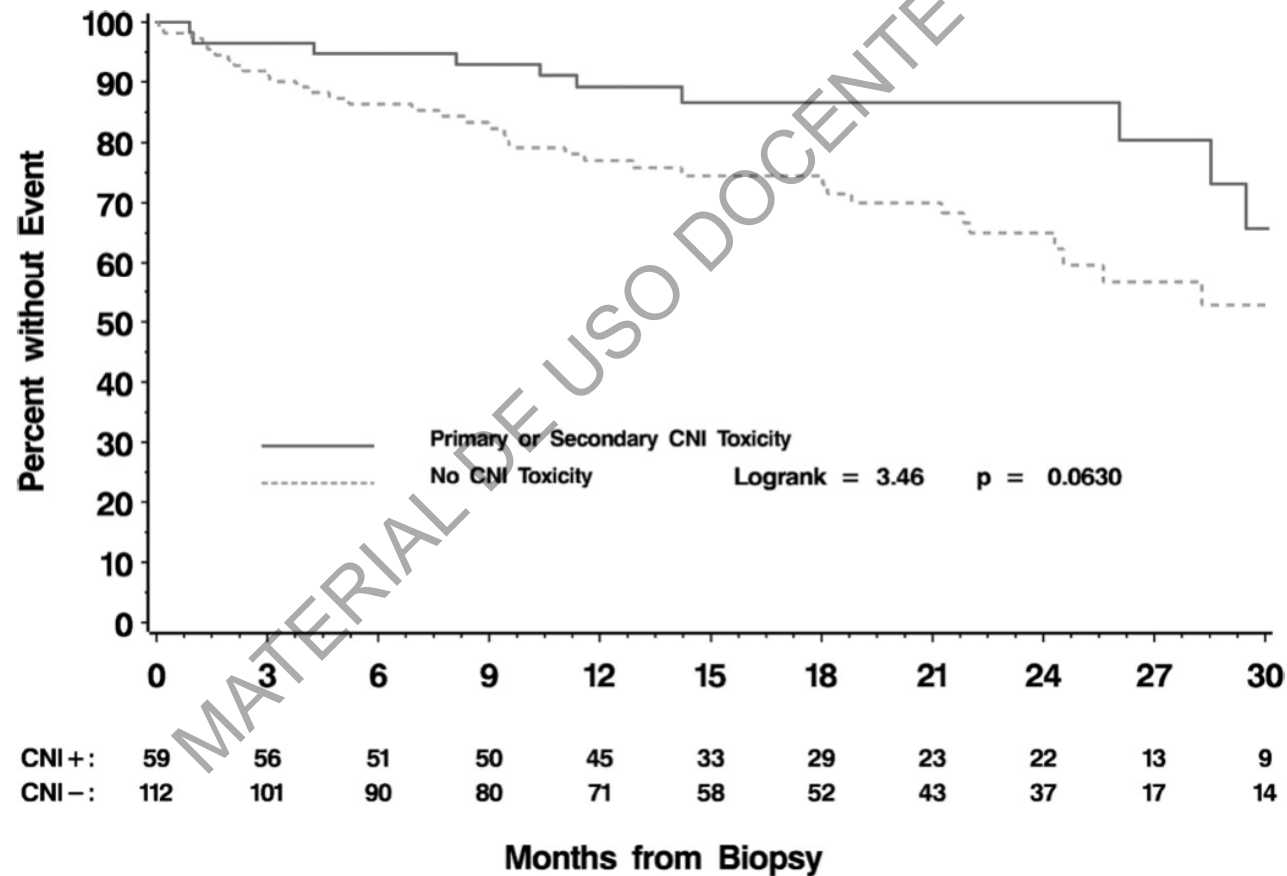
Pathogenesis of Chronic Allograft Nephropathy



Tubulointerstitial fibrosis is considered the final common mechanism leading to end-stage renal disease regardless of the initiating insult



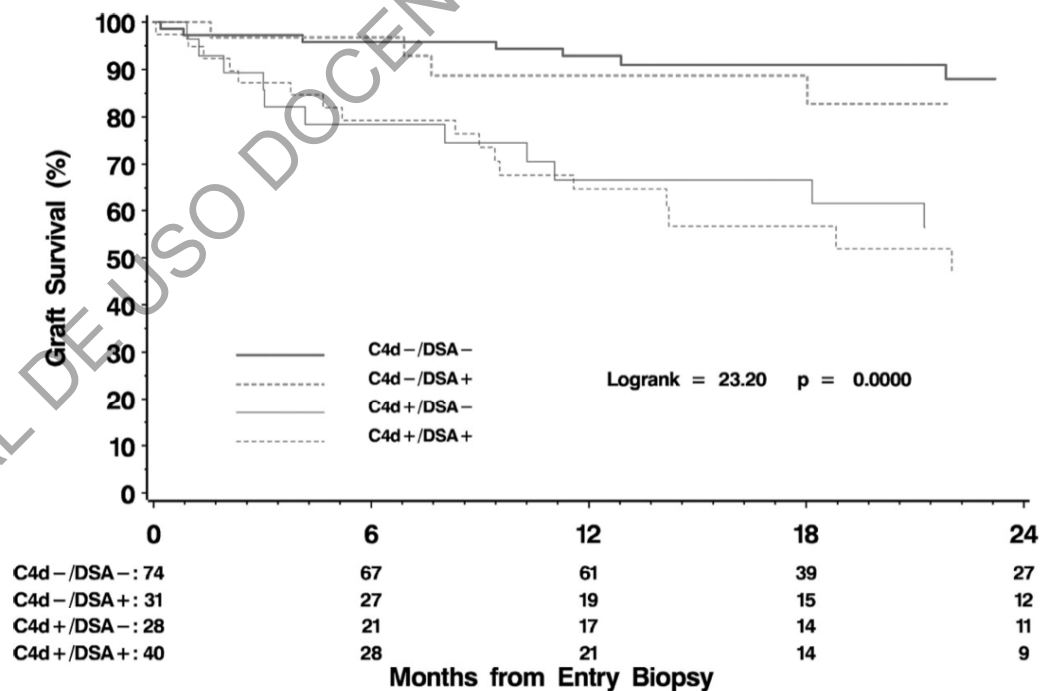
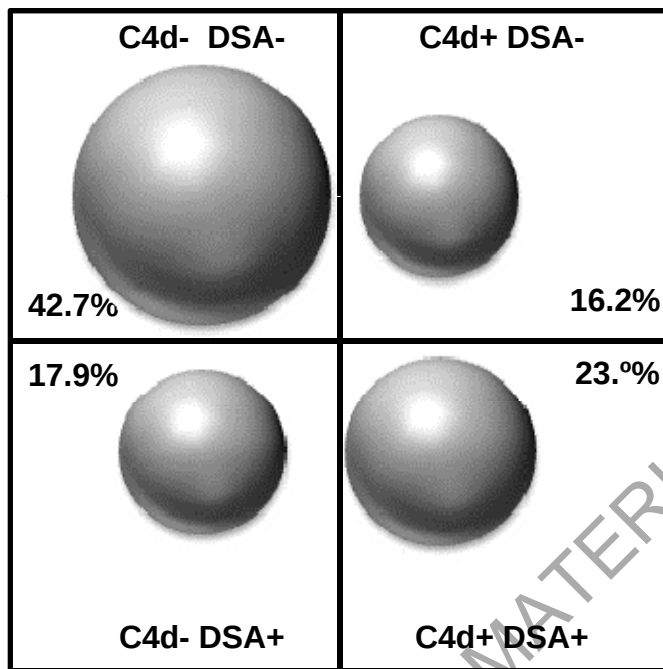
Evidence for Antibody-Mediated Injury as a Major Determinant of Late Kidney Allograft Failure: The Long-term Deterioration of Kidney Allograft Function (DeKAF)



Kaplan-Meier analysis of the impact of primary or secondary local diagnosis of calcineurin inhibitor (CNI) nephrotoxicity on kidney allograft survival after for-cause biopsy. Cross-sectional cohort (n=173)

Evidence for Antibody-Mediated Injury as a Major Determinant of Late Kidney Allograft Failure:

The Long-term Deterioration of Kidney Allograft Function (DeKAF)



173 renal for-cause biopsies in patients with deteriorating renal function 7.3 ± 6.0 years from transplant

Rechazo humoral crónico

Lesiones morfológicas sugestivas

Glomerulopatía del trasplante
Multilaminación de la membrana de los capilares peritubulares
Engrosamiento intimal y rotura de las elásticas
Fibrosis intersticial y atrofia tubular

Immunopatología

C4d en capilares peritubulares

Serología

Anticuerpos donante específicos (anti HLA u otros)

Revised (Banff 2013) classification of antibody-mediated rejection (ABMR) in renal allografts

Chronic, active ABMR; all three features must be present for diagnosis^{1,7}

1. Morphologic evidence of chronic tissue injury, including one or more of the following:
 - Transplant glomerulopathy (TG) (cg > 0)⁸, if no evidence of chronic thrombotic microangiopathy
 - Severe peritubular capillary basement membrane multilayering (requires EM)⁹
 - Arterial intimal fibrosis of new onset, excluding other causes¹⁰
2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:
 - Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
 - At least moderate microvascular inflammation (lg + ptc) ≥ 2⁵
 - Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated⁶
3. Serologic evidence of DSAs (HLA or other antigens)

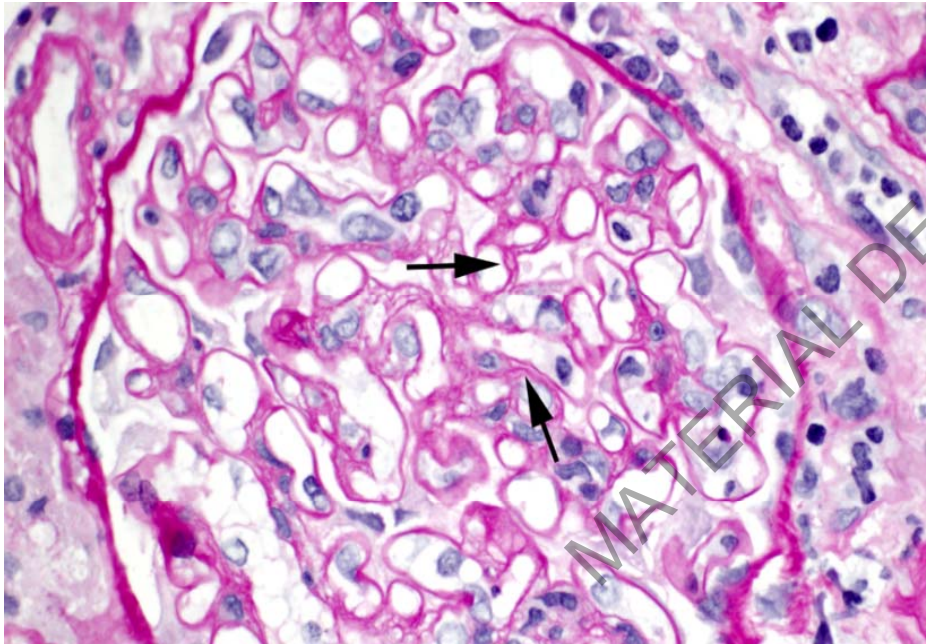
Revised (Banff 2013) classification of antibody-mediated rejection (ABMR) in renal allografts

C4d staining without evidence of rejection; all three features must be present for diagnosis¹¹

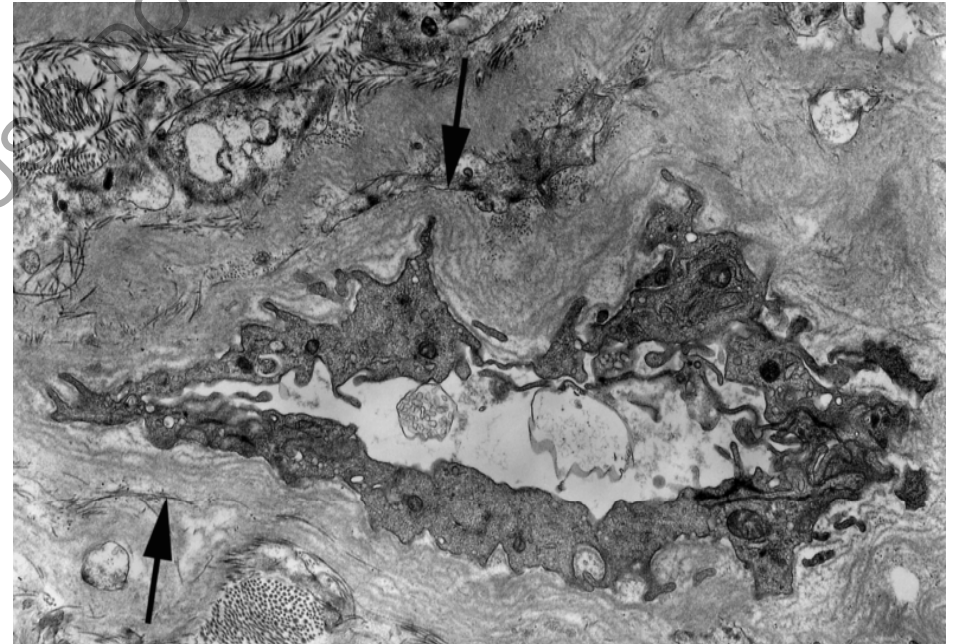
1. Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
 2. g = 0, ptc = 0, cg = 0 (by light microscopy and by EM if available), v = 0; no TMA, no peritubular capillary basement membrane multilayering, no acute tubular injury (in the absence of another apparent cause for this)
 3. No acute cell-mediated rejection (Banff 97 type 1A or greater) or borderline changes
-

Lesiones morfológicas sugestivas de rechazo crónico mediado por AC

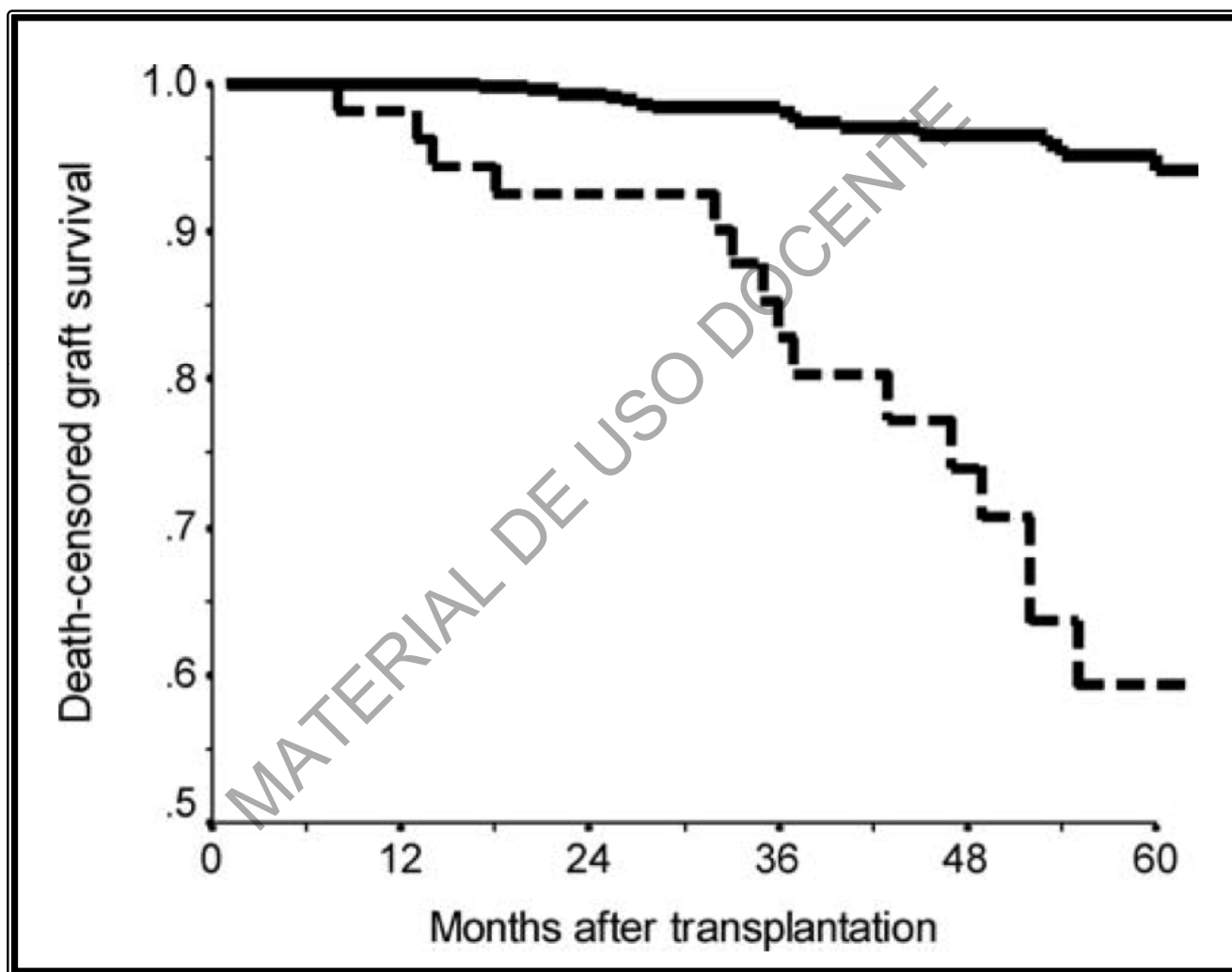
Glomerulopatía del trasplante



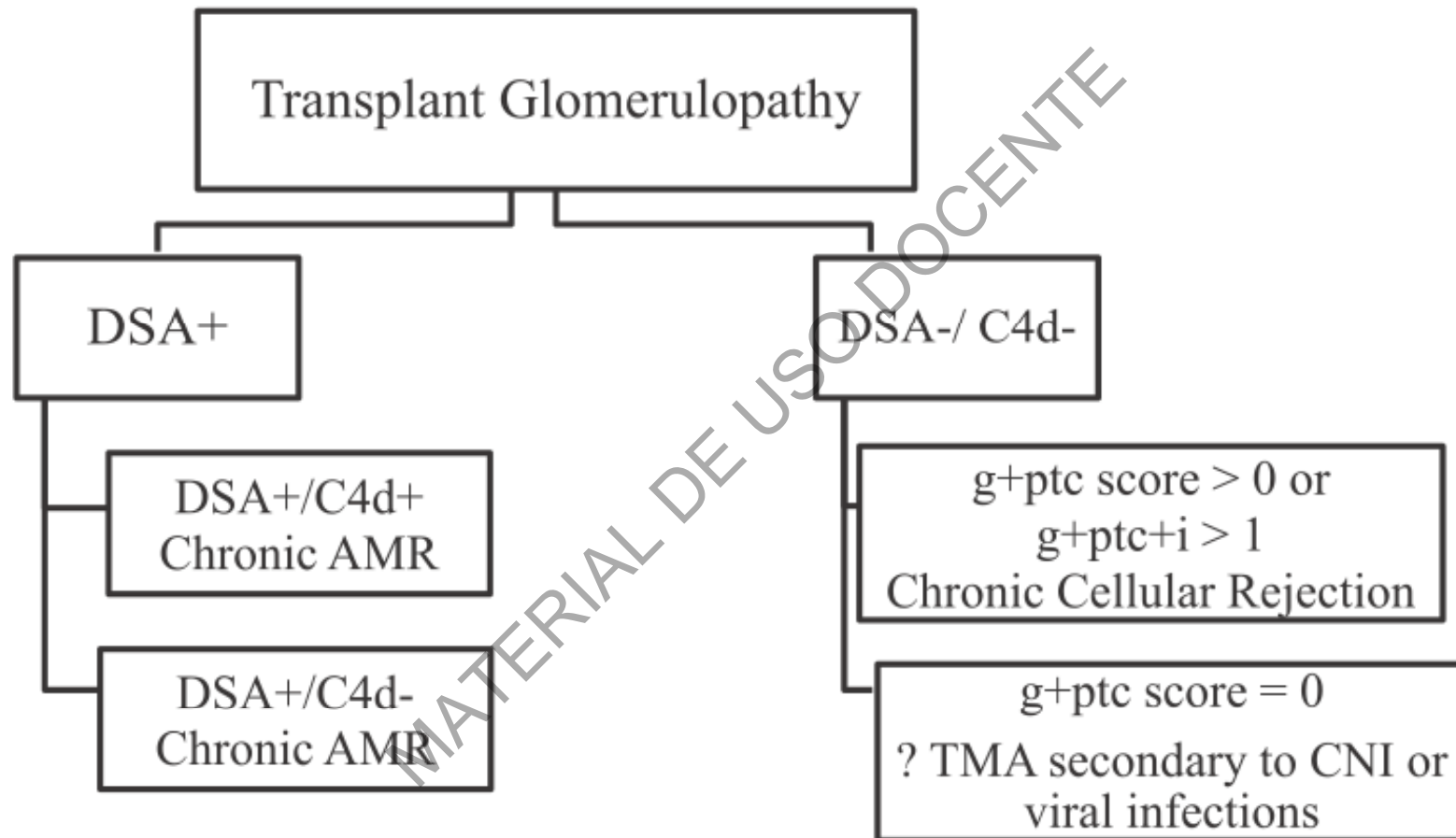
Reduplicación MB capilares peritubulares



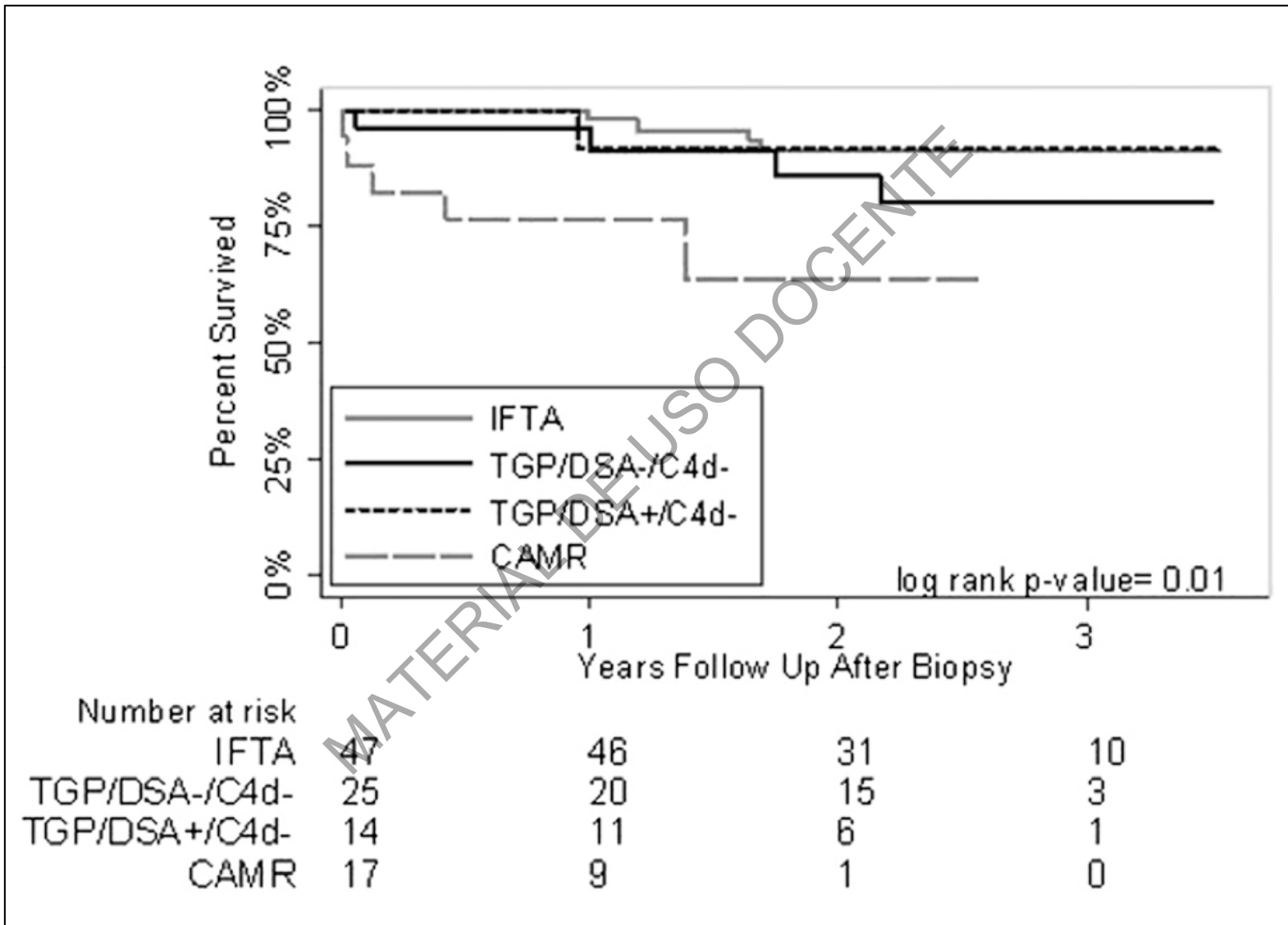
Kaplan-Meier plots of death-censored graft survival after conventional transplantation in patients without (—) and with TG (— — —).



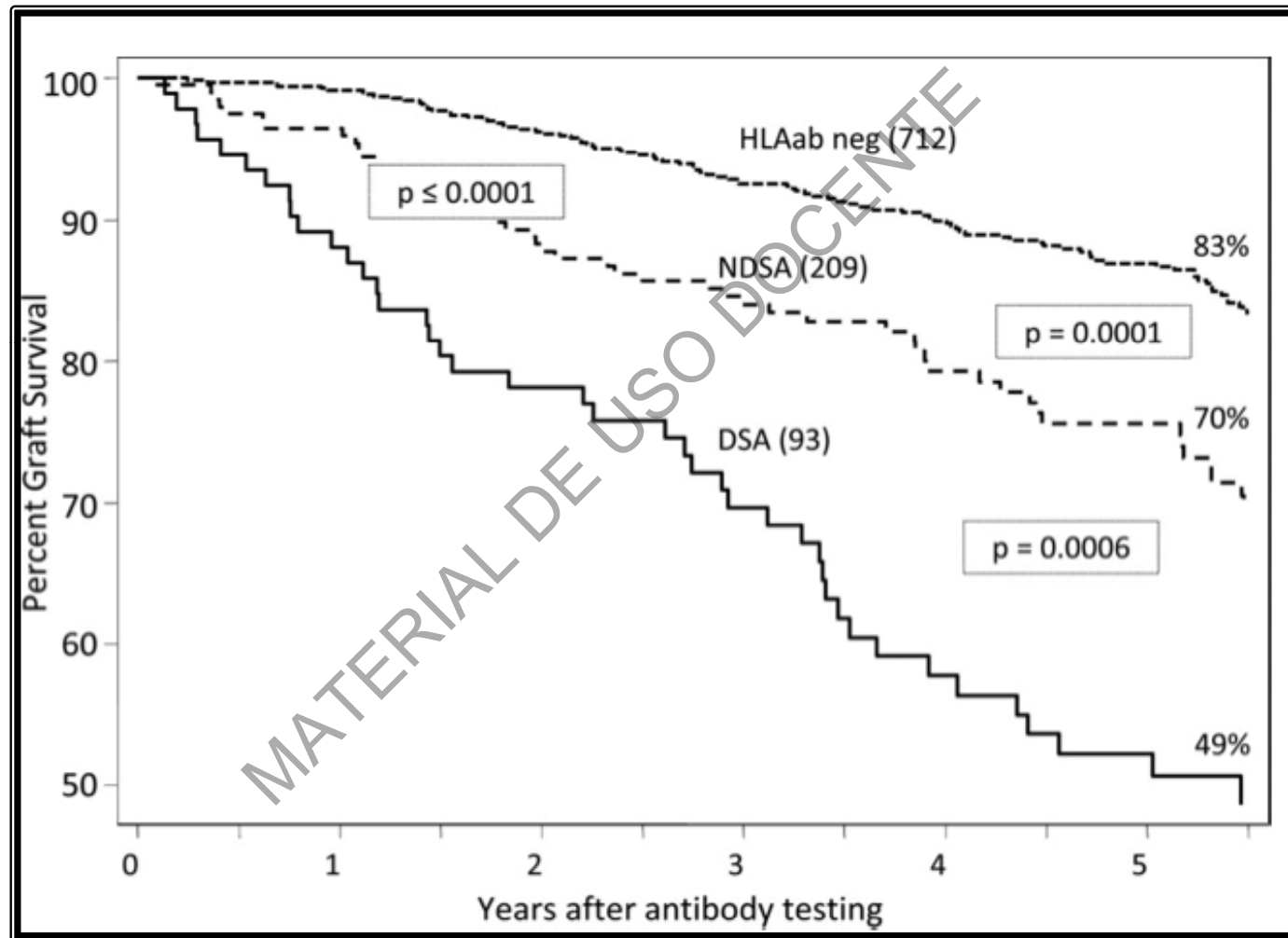
Hypothesis of the mechanisms leading to the development of transplant glomerulopathy



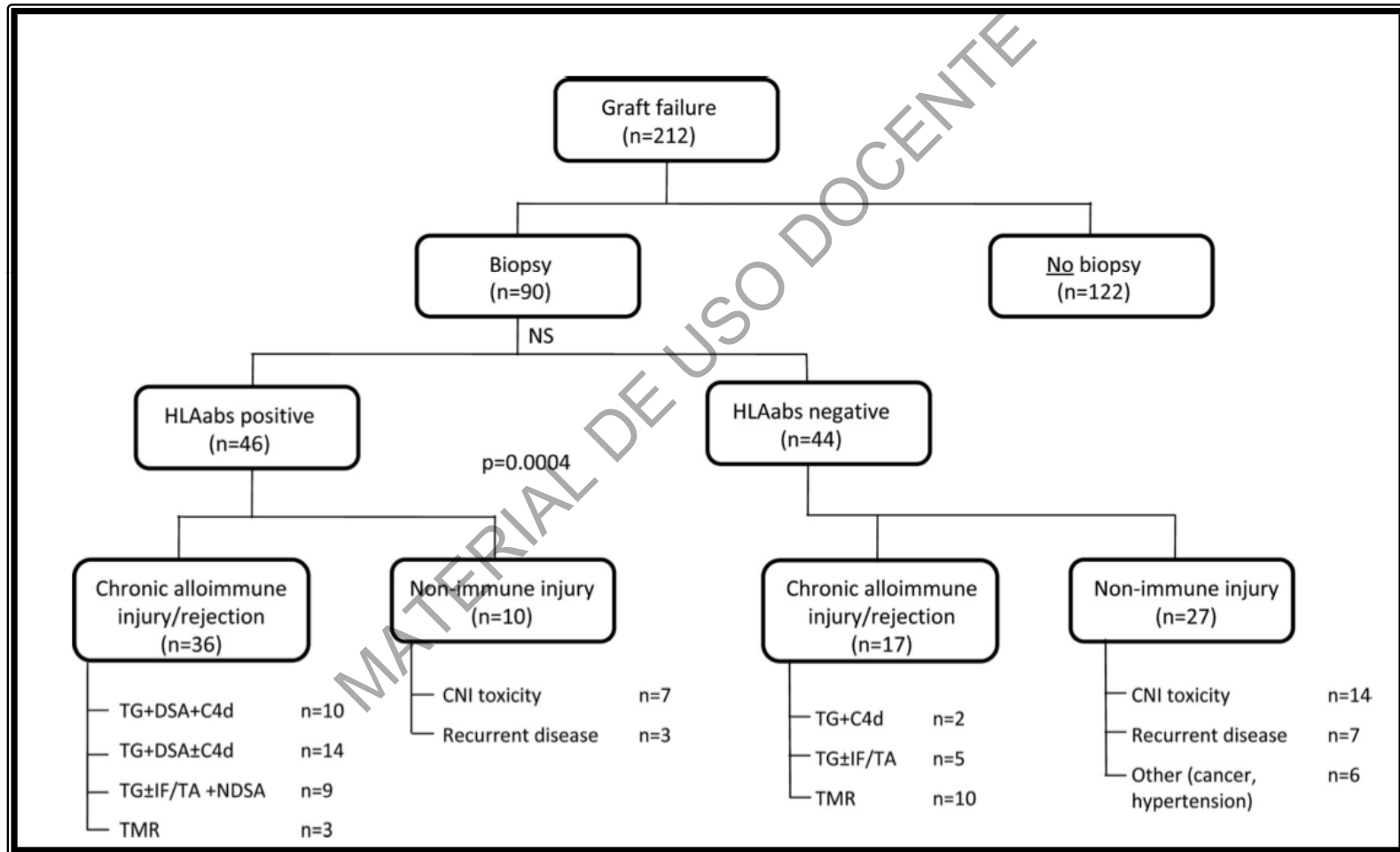
Kaplan-Meier death-censored graft survival stratified by histopathology



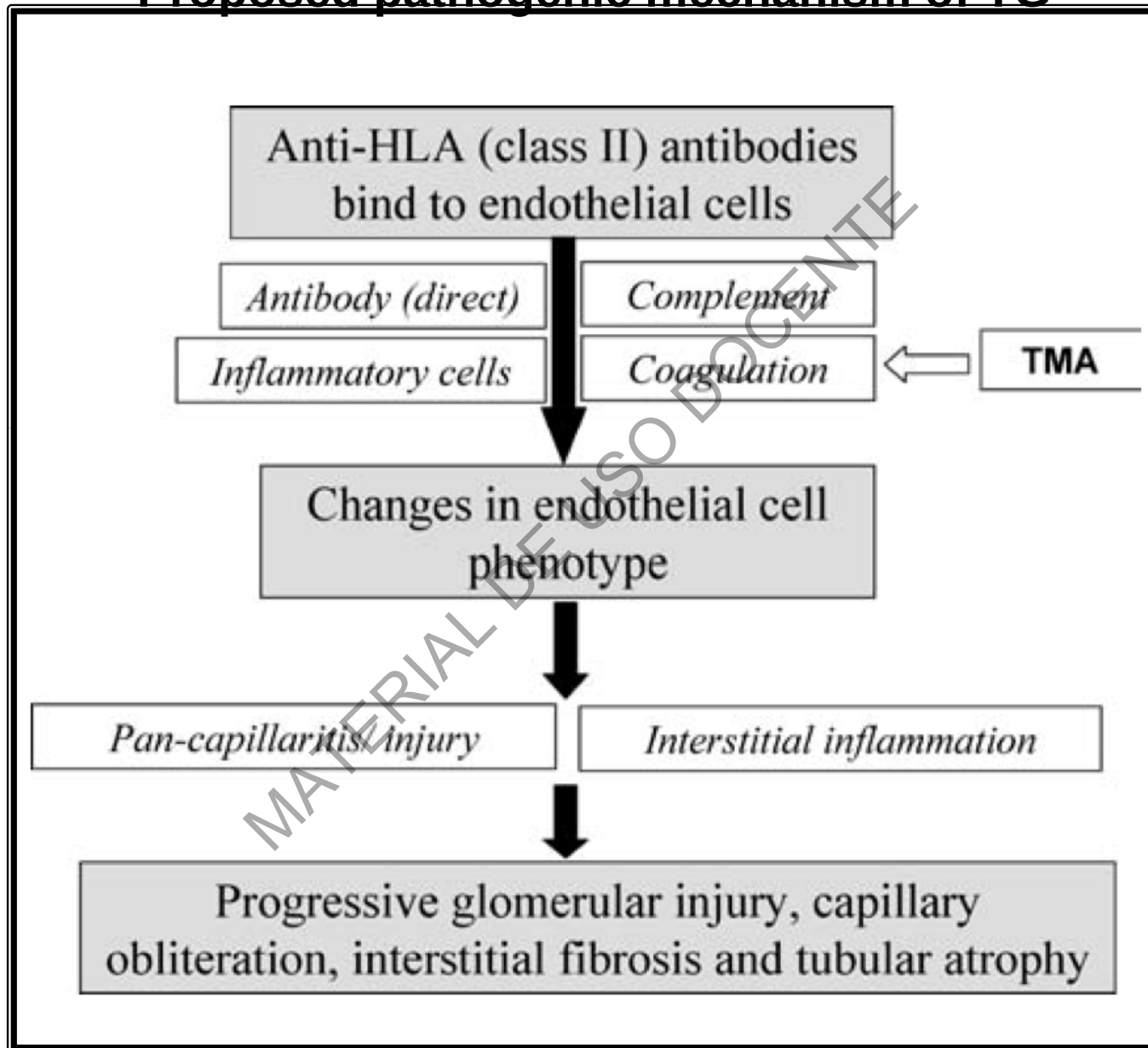
Anti-Human Leukocyte Antigen and Donor-Specific Antibodies Detected by Luminex Posttransplant Serve as Biomarkers for Chronic Rejection of Renal Allografts



Anti-Human Leukocyte Antigen and Donor-Specific Antibodies Detected by Luminex Posttransplant Serve as Biomarkers for Chronic Rejection of Renal Allografts



Proposed pathogenic mechanism of TG



Overlapping pathways to transplant glomerulopathy: chronic humoral rejection, hepatitis C infection, and thrombotic microangiopathy

Seema Baid-Agrawal¹, Alton B. Farris III², Manuel Pascual³, Shamila Mauiyyedi⁴, Mary Lin Farrell⁵, Nina Tolkoﬀ-Rubin⁵, A. Bernard Collins⁶, Ulrich Frei¹ and Robert B. Colvin⁶

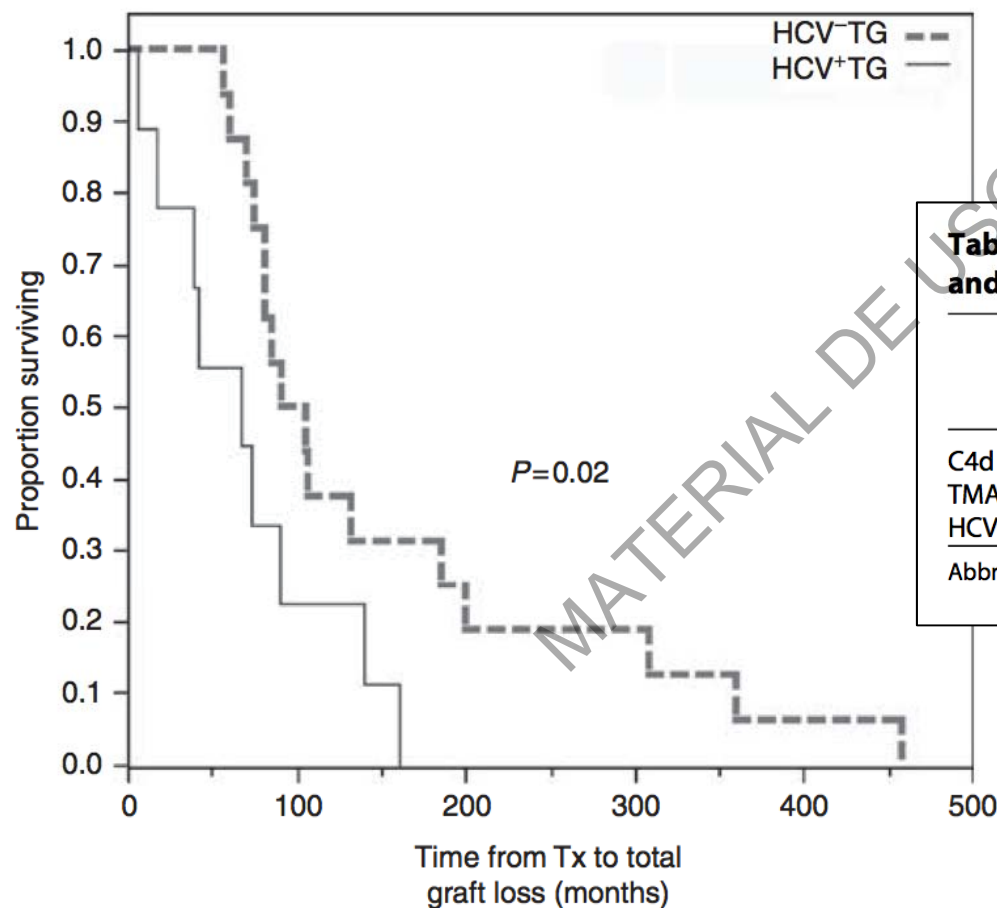


Table 3 | Multivariate analysis of clinicopathological factors and time to graft loss

	Likelihood ratio (<i>P</i> -value) based on proportional hazards (Cox) fit	Likelihood ratio (<i>P</i> -value) based on parametric survival fit
C4d	0.82 (<i>P</i> =0.36)	1.86 (<i>P</i> =0.17)
TMA	0.14 (<i>P</i> =0.71)	0.29 (<i>P</i> =0.59)
HCV	4.56 (<i>P</i> =0.03)	5.06 (<i>P</i> =0.02)

Abbreviations: HCV, hepatitis C virus; TMA, thrombotic microangiopathy.

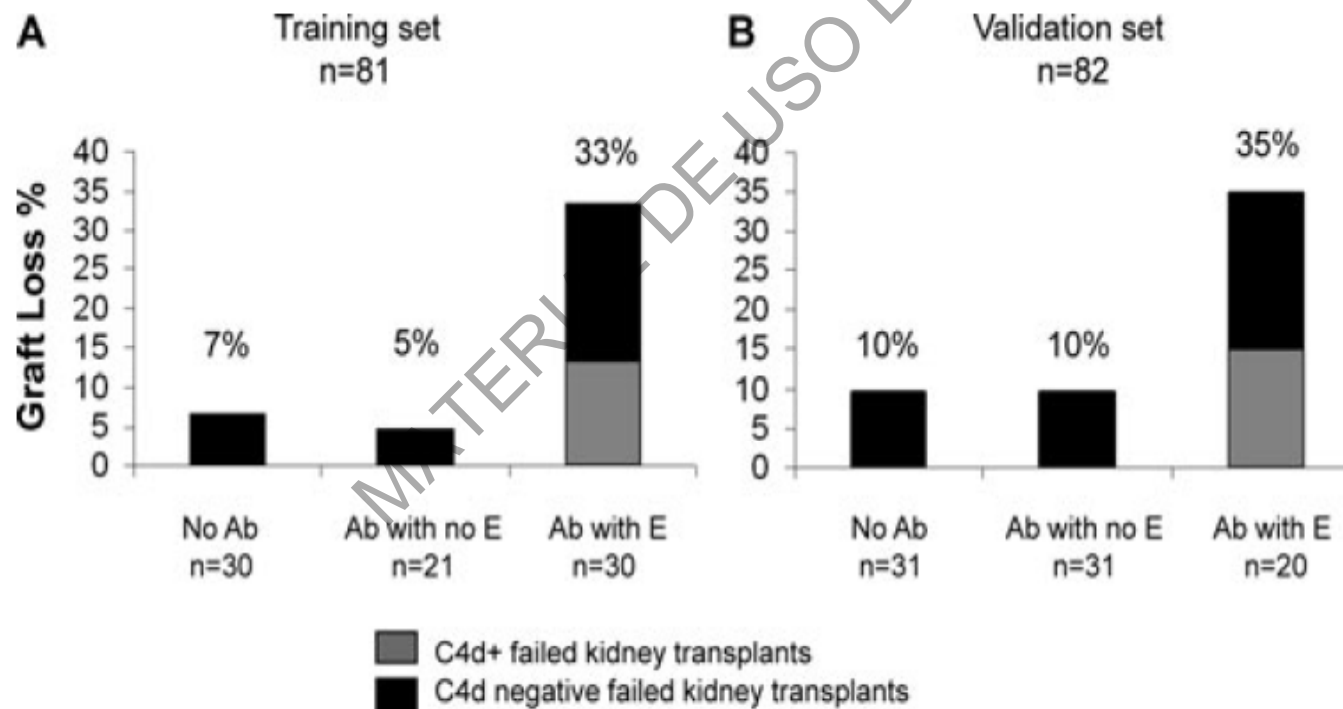
Rechazo humoral C4d negativo

MATERIAL DE USO DOCENTE

C4d en biopsias de vigilancia e indicación en Tx ABO y HLA incompatible

	Seguimiento	Indicación	Correlación con ptc
ABO inc (%)	80	59	NO
HLA inc (%)	26	60	YES

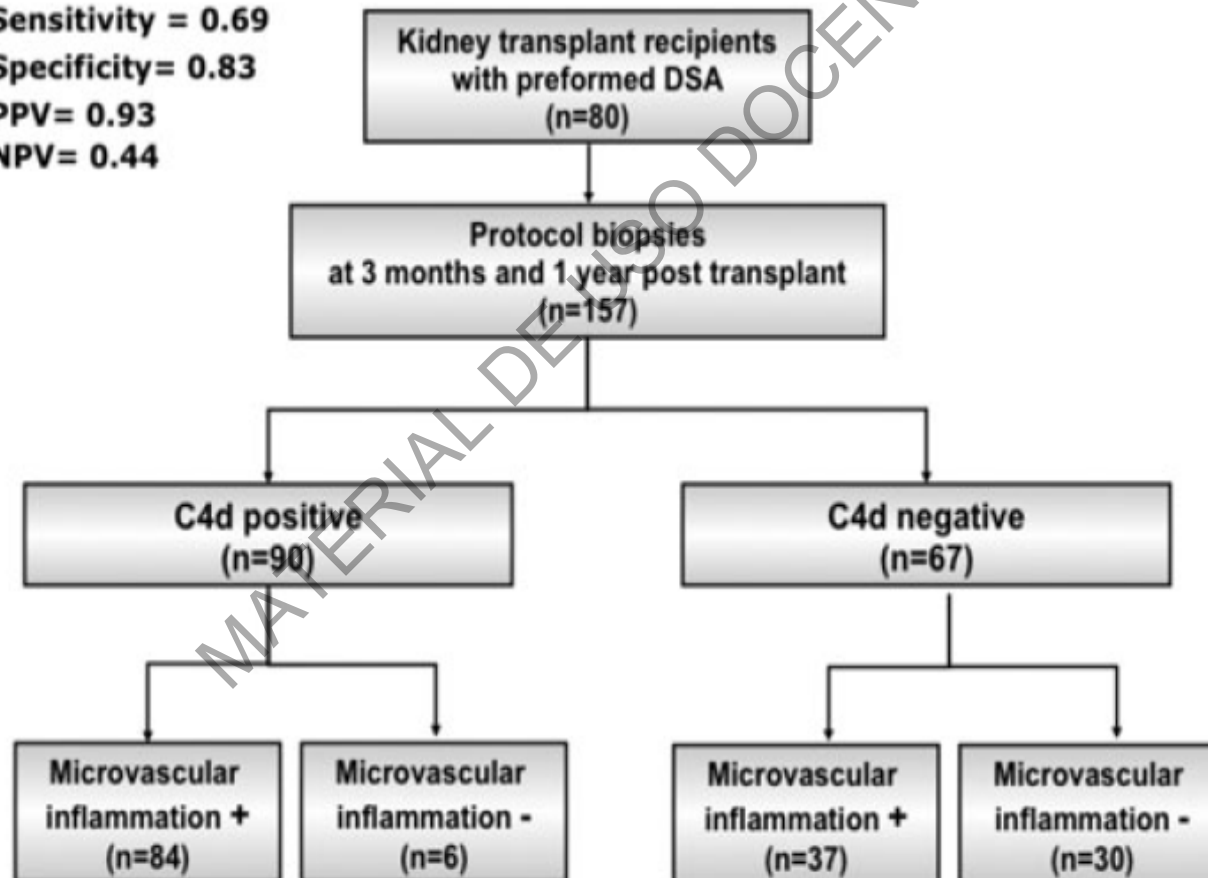
ENDAT: “endothelial associated transcripts”, C4d, MI y pérdida del injerto



C4d, MI y DSA en biopsias de seguimiento

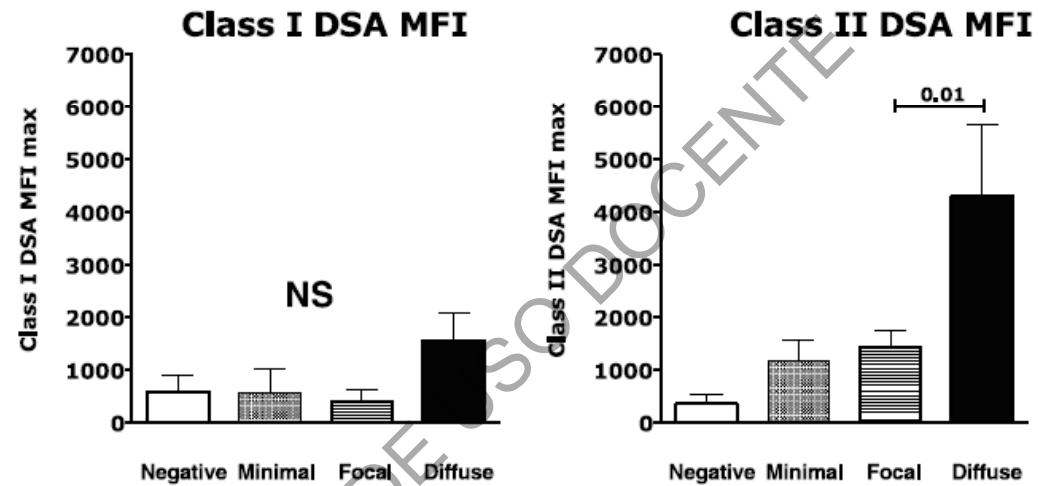
n=157 Bx de protocolo de 80 pacientes DSA + que reciben Tx de cadáver

Sensitivity = 0.69
Specificity = 0.83
PPV = 0.93
NPV = 0.44

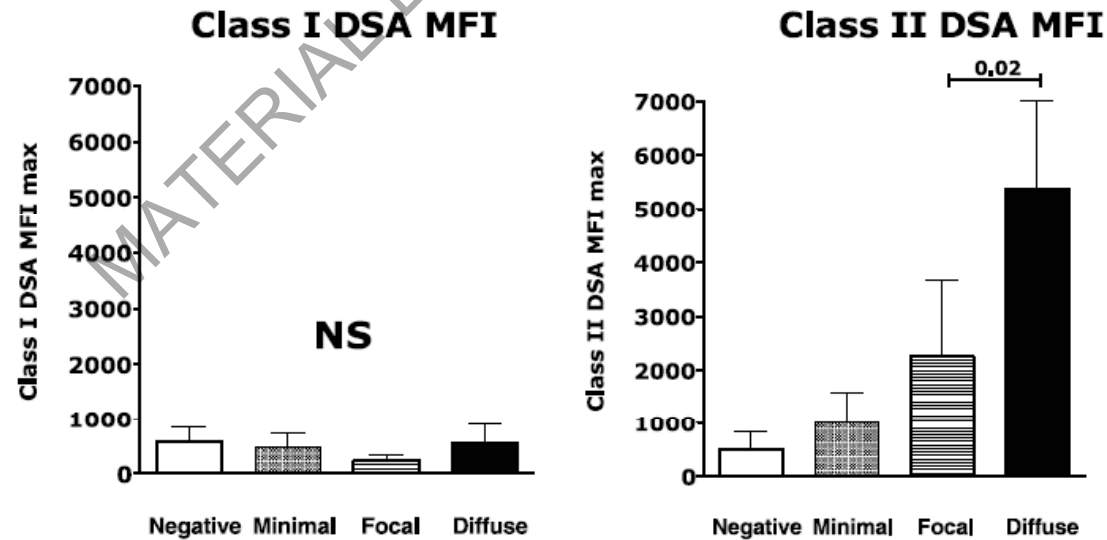


Relación entre MFI max y C4d

3 meses

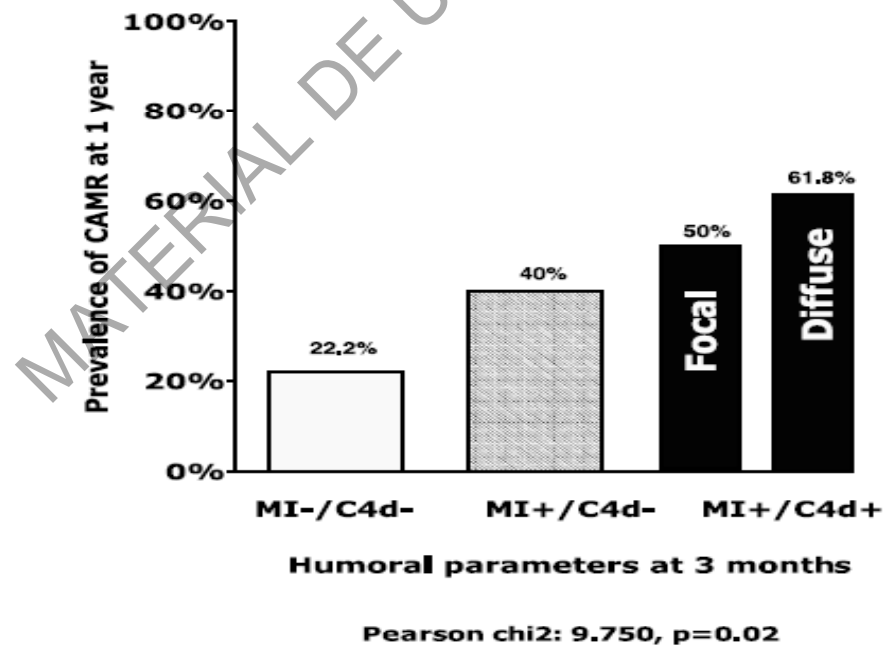


12 meses



Probabilidad de Rechazo humoral crónico 1 a en función de MI y C4d a los 3m

Variable	RR	95CI	p
MI	4.0	1.0-16.0	0.05
DSA II	4.1	1.1-15.0	0.03



Rechazo humoral subclínico

MATERIAL DE USO DOCENTE

Rechazo humoral subclínico

	N	C4d > 50%	C4d 25-50%
Indicación	377	12.2 %	8.5%
Seguimiento	551	2.0%	2.4%

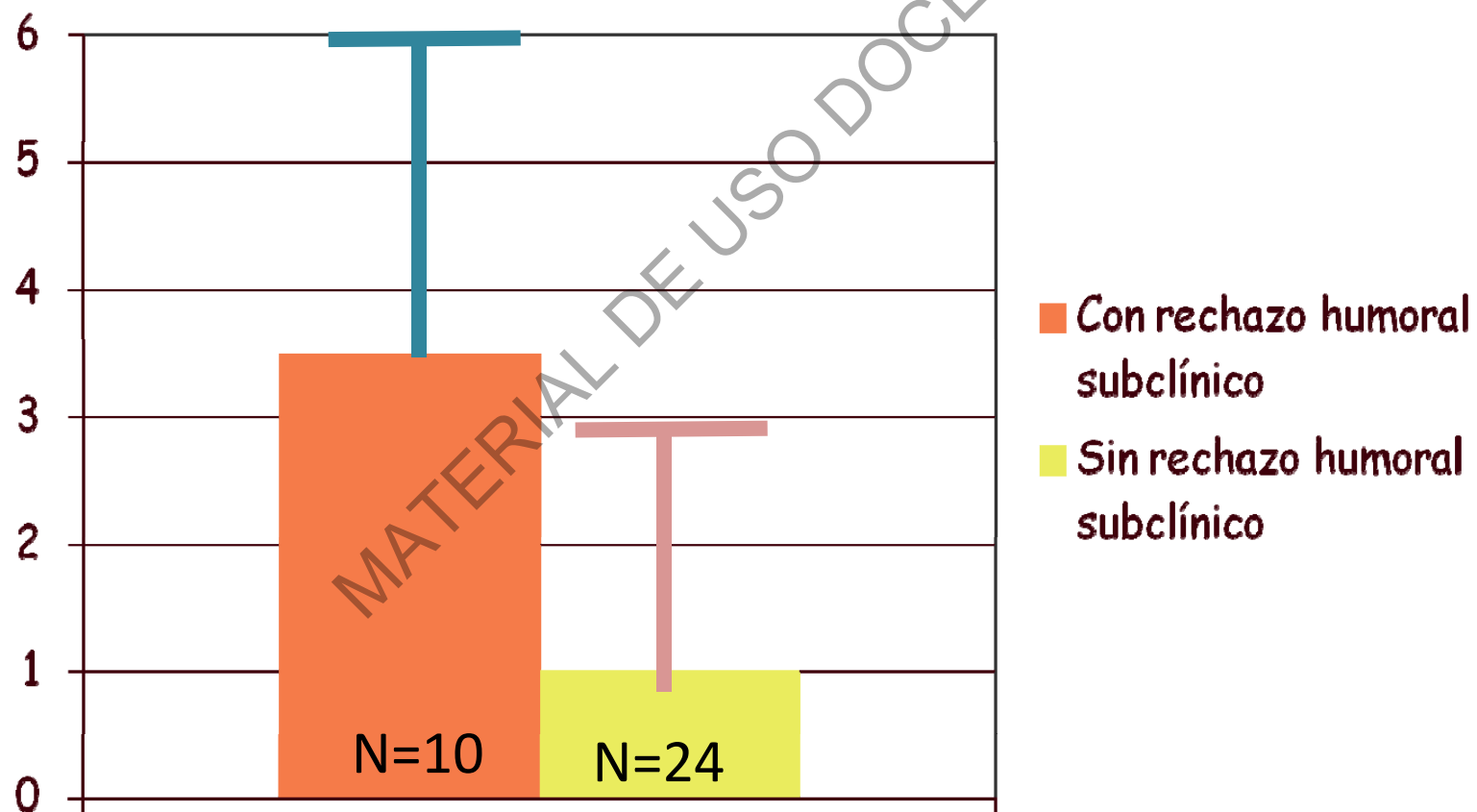
“correlación entre C4d y capilaritis”

Rechazo humoral subclínico y progresión del daño crónico

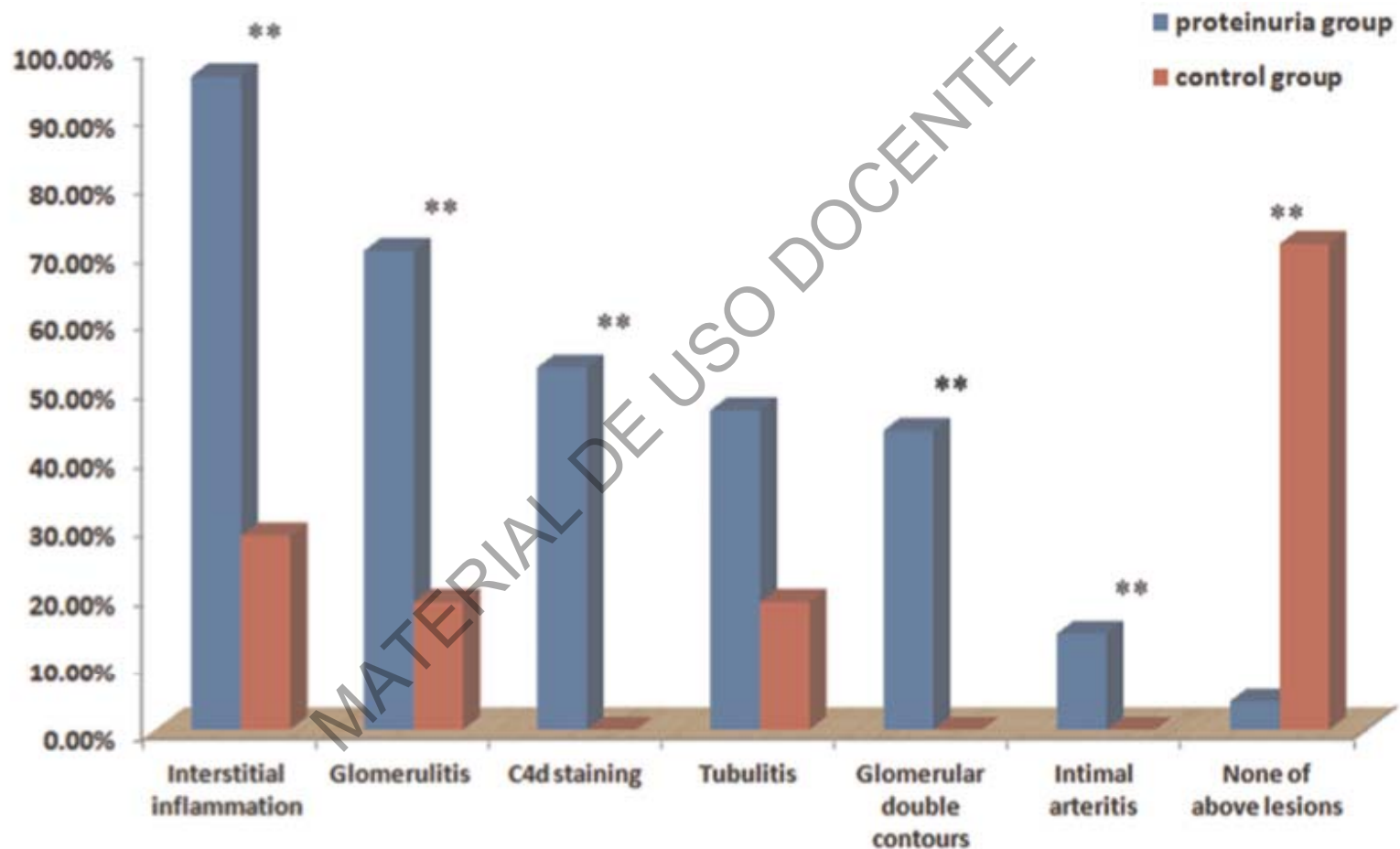
Tx donante vivo, cross match +, tto desensibilización: PF + Ig

Seguimiento 1a , biopsias 1, 3, 6, 12 m (al menos Bx 3 y 12 m)

Score crónico de Banff a los 12 m

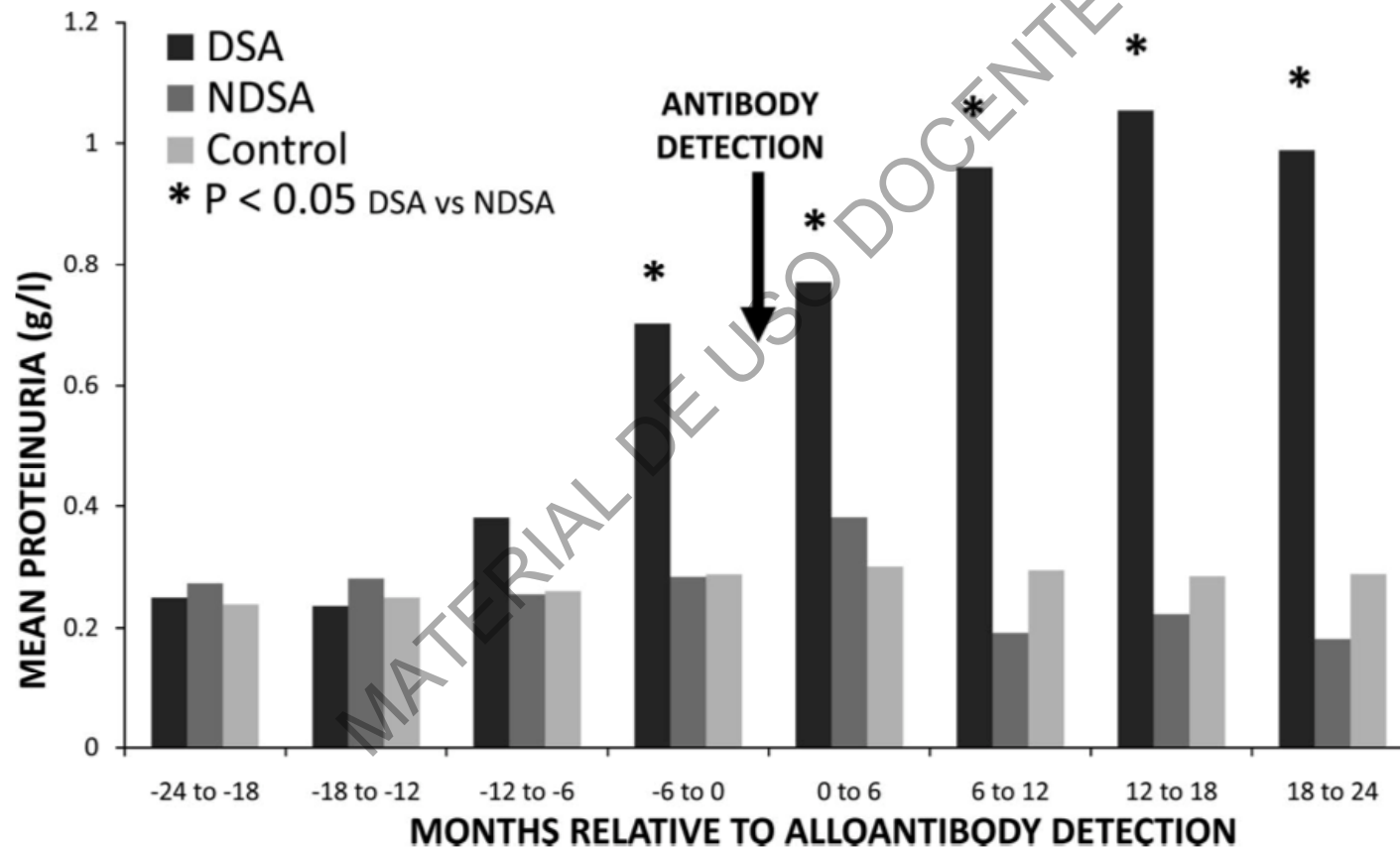


Prevalence of histological lesions related to immune activity in patients with proteinuria (> 400 mg/d)

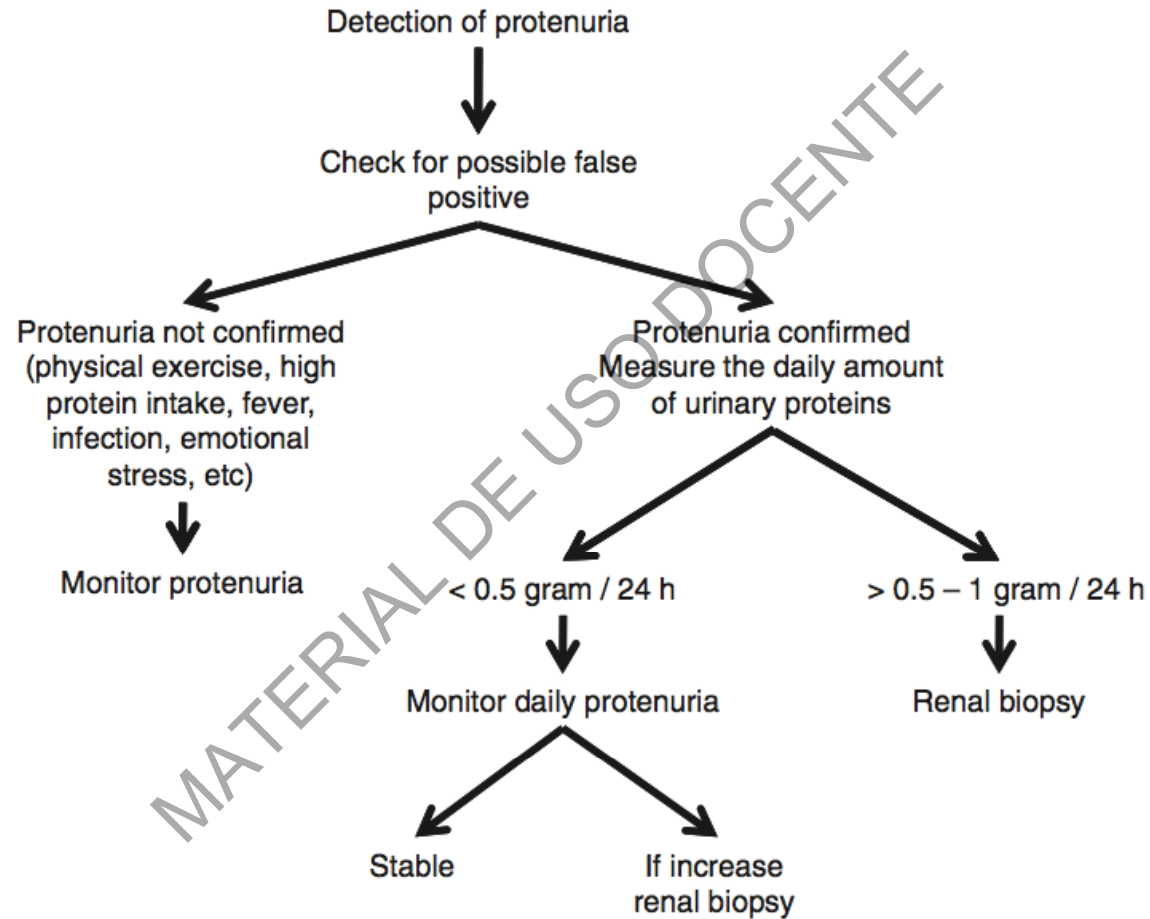


Sun O et al, PLoS ONE 2012, 7(5): e36654.

Natural History of Proteinuria in Renal Transplant Recipients Developing De Novo Human Leukocyte Antigen Antibodies



A diagnostic approach to posttransplant proteinuria



La biopsia pre-implante ayuda a interpretar los hallazgos

TABLE 3. Incidences of histopathological findings in 102 renal allografts at the time of transplantation (implant) and 1 year after transplantation

Histological findings	Implant specimen (%) n=102	1-Year specimen (%) n=102	
Interstitialium			
<i>Fibrosis</i>	42	85	$P<0.05$
<i>Inflammation</i>	3	88	$P<0.05$
Tubuli			
<i>Atrophy</i>	6	67	$P<0.05$
Isometric vacuolization	8	3	NS
Anisometric vacuolization	60	9	$P<0.05$
Pigmentation	21	0	$P<0.05$
Basement-membrane thickening	24	68	$P<0.05$
Vessels			
<i>Intimal proliferation</i>	10	22	$P<0.05$
Sclerosis	16	24	NS
Hyalinosis	38	20	$P<0.05$
Glomeruli			
<i>Mesangial matrix increase</i>	18	39	$P<0.05$
<i>Sclerosis</i>	30	29	NS

All other pathological findings occurred in fewer than 10% of samples. Histopathological findings in *italics* are elements of CADI.

Histological alterations associated with chronic rejection are already present at the time of transplantation. The lack of a baseline biopsy may difficult the interpretation of the origin of the lesions.

SRK Lehtonen, Transplantation 2001, 72(6): 1138-1144

Tratamiento del rechazo mediado por anticuerpos

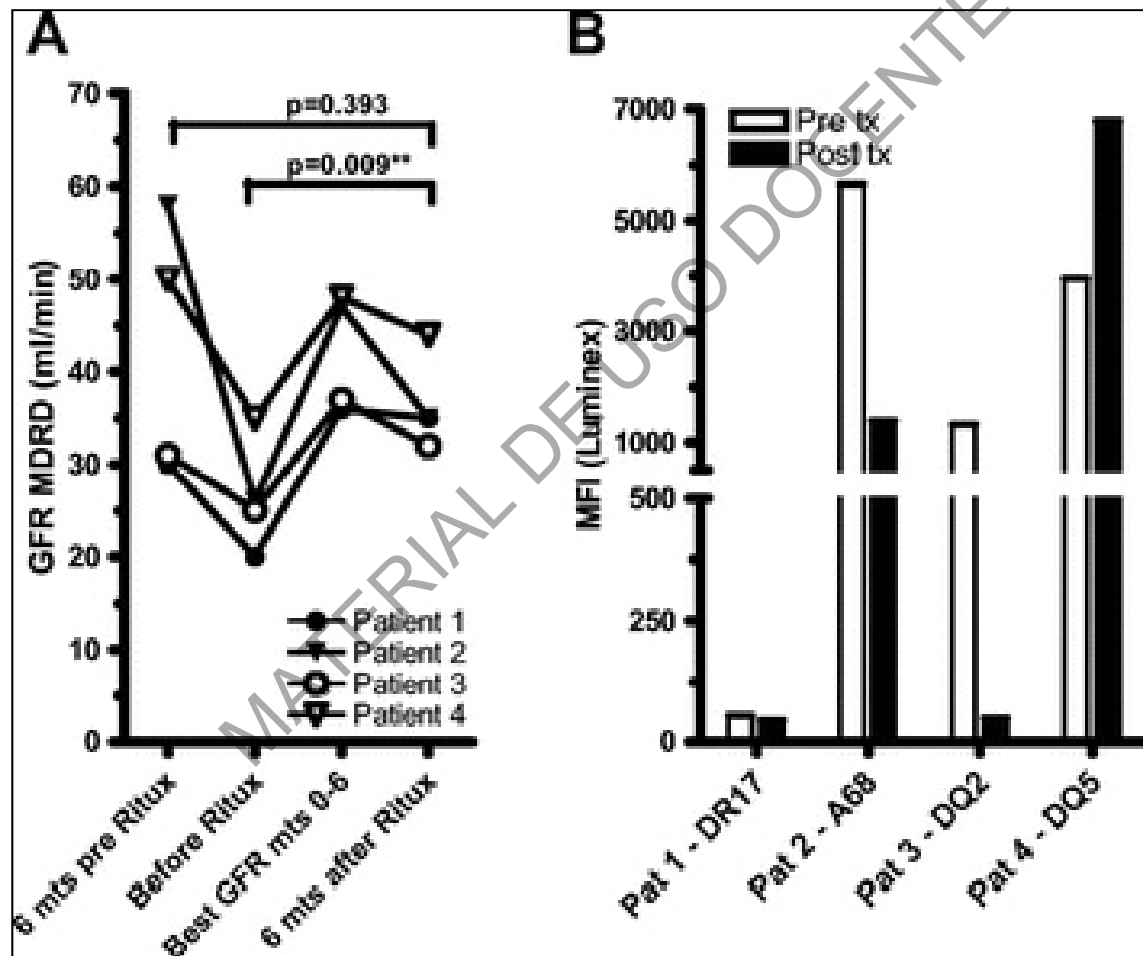
- Eliminación de anticuerpos circulantes:
 - recambios plasmáticos, inmunoadsorción
- Inhibición de anticuerpos residuales:
 - inmunoglobulinas intravenosas, micofenolato mofetil
- Supresión de la producción de anticuerpos o depleción de linfocitos B:
 - corticosteroides, rituximab, ATG, esplenectomía
- Apoptosis/depleción de células plasmáticas:
 - inhibidores de proteosoma (bortezomib)
- Inhibición de la activación terminal del complemento:
 - anticuerpos anti-C5 (eculizumab)

Rituximab and Intravenous Immunoglobulin Treatment of Chronic Antibody-Mediated Kidney Allograft Rejection.

Fehr, Thomas; Rusi, Barbara; Fischer, Andreas; Hopfer, Helmut; Wuthrich, Rudolf; Gaspert, Ariana

Transplantation. 87(12):1837-1841, June 27, 2009.

DOI: 10.1097/TP.0b013e3181a6bac5



Eculizumab Therapy for Chronic Antibody-Mediated Injury in Kidney Transplantation: An Interim Assessment. S. Kulkarni,¹ N. Kirkles-Smith,² R. Tomlin,¹ R. Formica,³ G. Moeckel,⁴ J. Pober.² *1Surgery, Yale University School of Medicine, New Haven, CT; 2Immunobiology, Yale University School of Medicine, New Haven, CT; 3Medicine, Yale University School of Medicine, New Haven, CT; 4Pathology, Yale University School of Medicine, New Haven, CT.*

Six kidney transplant recipients (2 control, 4 treatment), who had developed de novo DSA and had worsening renal function completed 6 months of either eculizumab therapy or observation, as a part of an ongoing clinical study to test if eculizumab would ameliorate antibody-mediated injury.

Conclusion: Interim assessment of transplant patients with de novo DSA and worsening renal function show an apparent stabilization in their renal function with eculizumab therapy. However, increased endothelial cell mRNAs, possibly indicative of CAMR, may not be diminished by eculizumab therapy.

This Provisional PDF corresponds to the article as it appeared upon acceptance. Fully formatted PDF and full text (HTML) versions will be made available soon.

Bortezomib in late antibody-mediated kidney transplant rejection (BORTEJECT Study): study protocol for a randomized controlled trial

Trials 2014, **15**:107 doi:10.1186/1745-6215-15-107

Table 4 Study endpoints

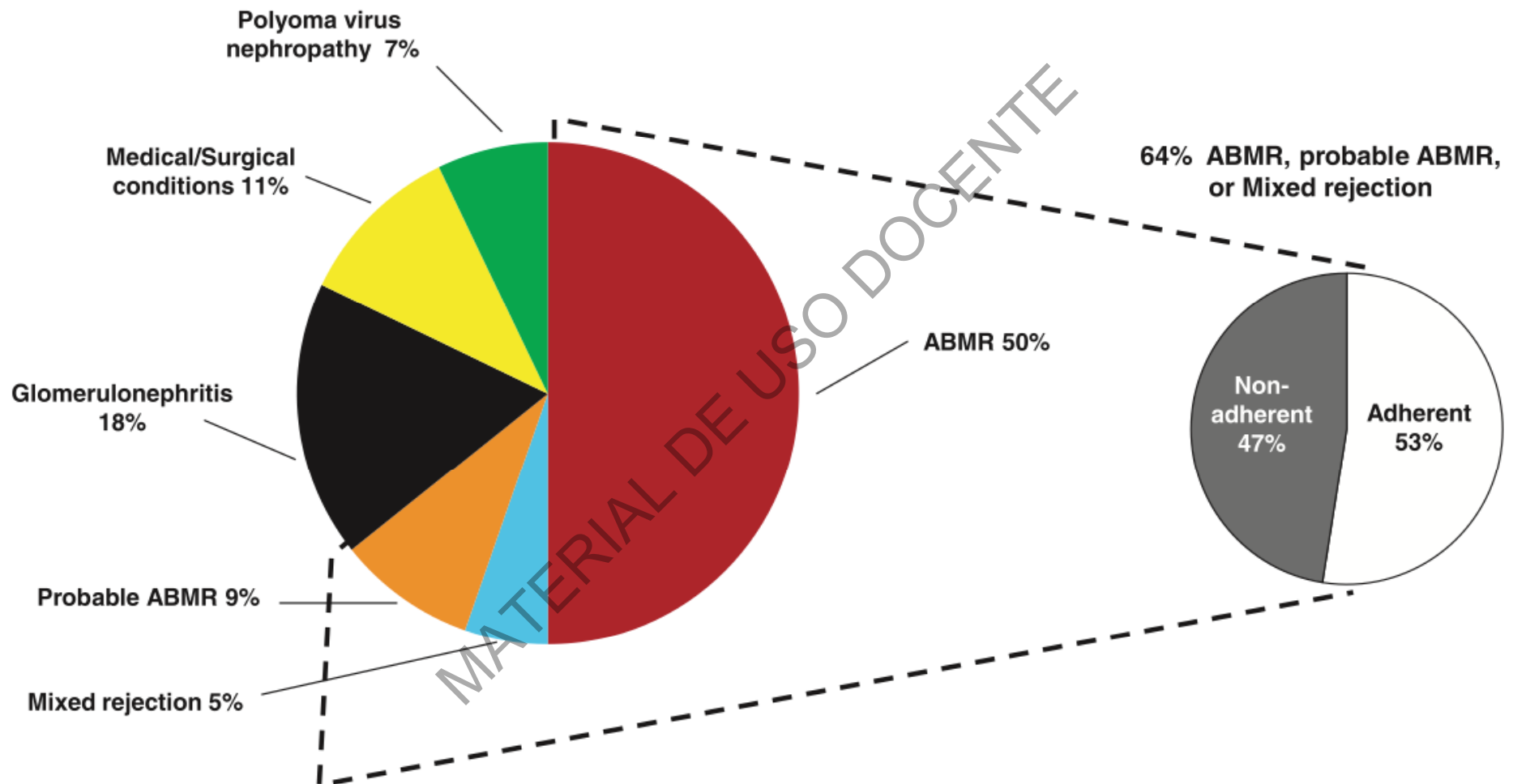
Primary outcome	Slope of eGFR over 24 months
Secondary outcomes	Graft and patient survival at 24 months
	Measured GFR (Cr-51-EDTA method) at 24 months
	DSA at 6, 12, 18, and 24 months
	Mean fluorescence intensity levels
	Number of human leukocyte antigen specificities
	Urinary protein excretion (protein/creatinine ratio) at 6, 12, 18, and 24 months
	Occurrence of biopsy-proven acute rejection necessitating rejection treatment
	Acute AMR score in a protocol biopsy performed at 24 months
	Chronic AMR score in a protocol biopsy performed 24 months

Table 1. Efficacy and side effects of interventions for the prevention or treatment of antibody-mediated graft injury

	Desensitization protocols	Acute ABMR treatment	Chronic ABMR treatment	Potential adverse events	Cost
1. PLEX	+	+	±	Hypotension, bleeding, hypovolemia	+
2. IVIG	+	+	±	Allergy, headache, myalgia, fever	+
3. Rituximab (Rx)	++	++	+?	Infections, neutropenia, infusion reactions	++
4. Bortezomib (Bx)	ND	+++	+?	Myelosuppression, neuropathy GI toxicity	++
5. Eculizumab (Ex)	NA	++	+?	Meningococcal infection, hypertension	+++
6. Splenectomy (Sx)	++	++	+?	Infections, thrombocytosis	+
7. PLEX + IVIG	++	++	±	Additive	Additive
8. IVIG + Rx	++	++	+		
9. PLEX + IVIG + Rx	+++	+++	NA		
10. PLEX + IVIG + Sx	+++	+++	+?		
11. PLEX + IVIG + Rx + Bx	ND	+++	+		
12. PLEX + IVIG + Rx + Ex	NA	++++	ND		

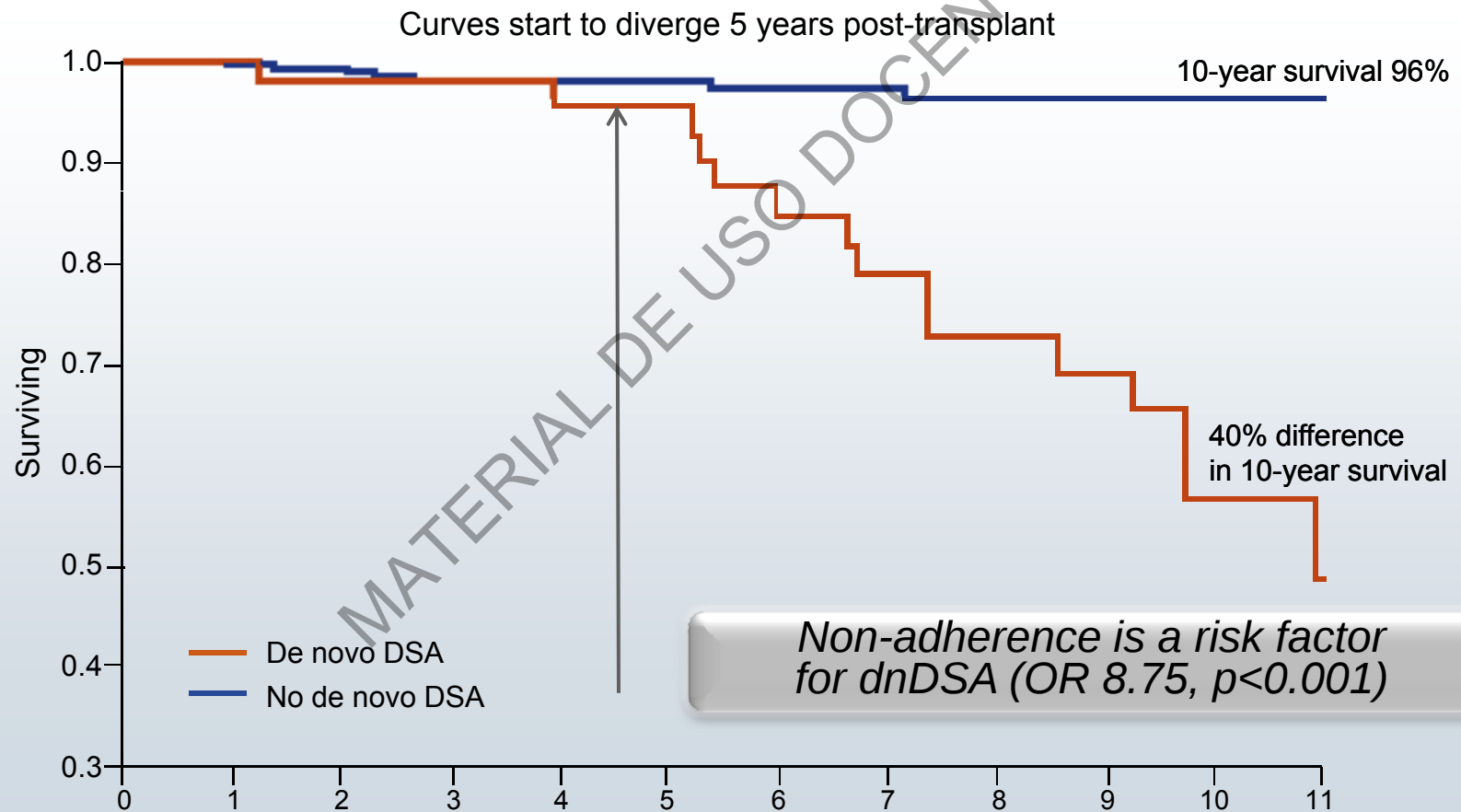
ND, no data; NA, not applicable; ±, occasional; ?, few data, not exactly known.

Understanding the Causes of Kidney Transplant Failure: The Dominant Role of Antibody-Mediated Rejection and Nonadherence

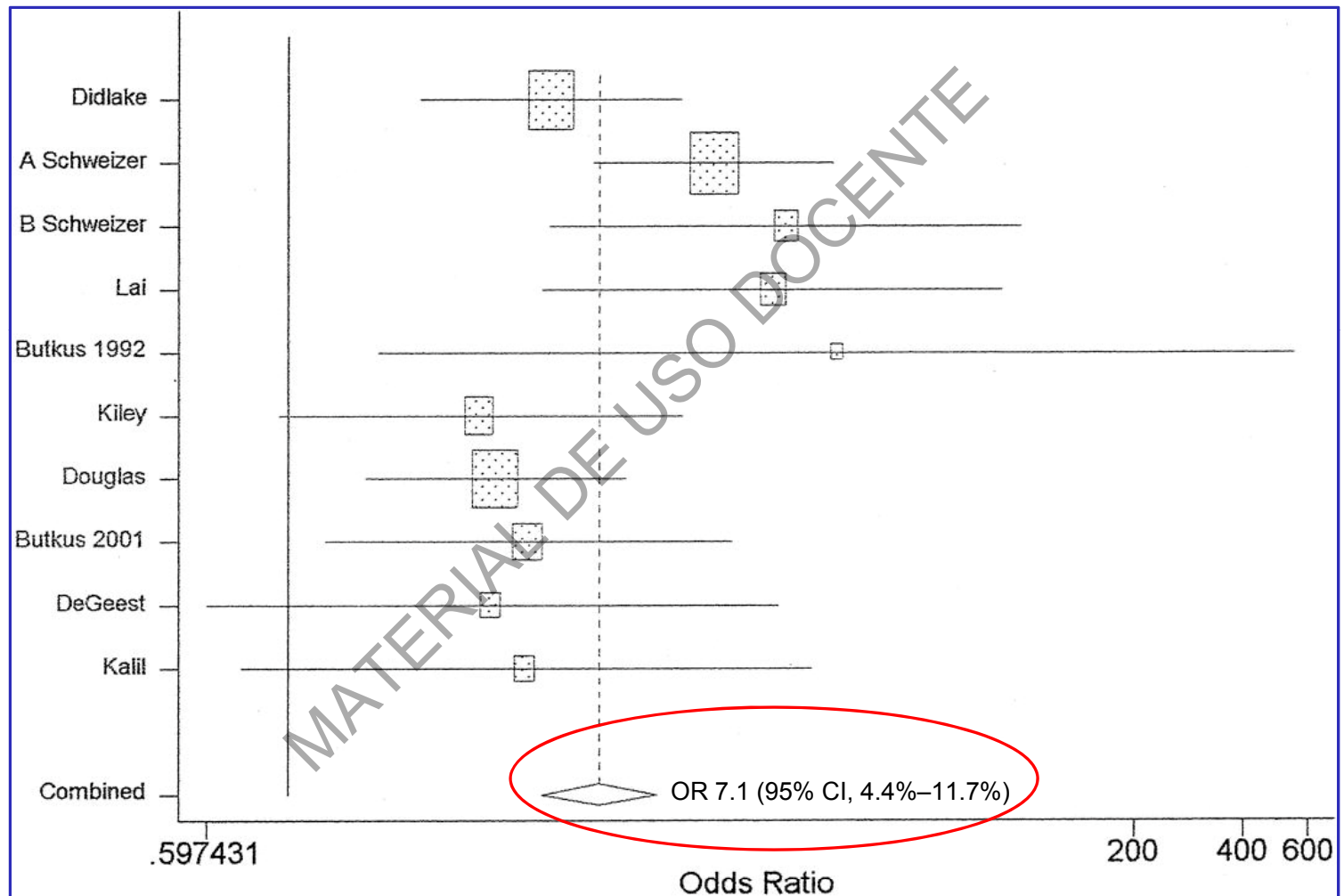


DSA have been associated with a decrease in graft survival with a strong association between non-adherence & dnDSA

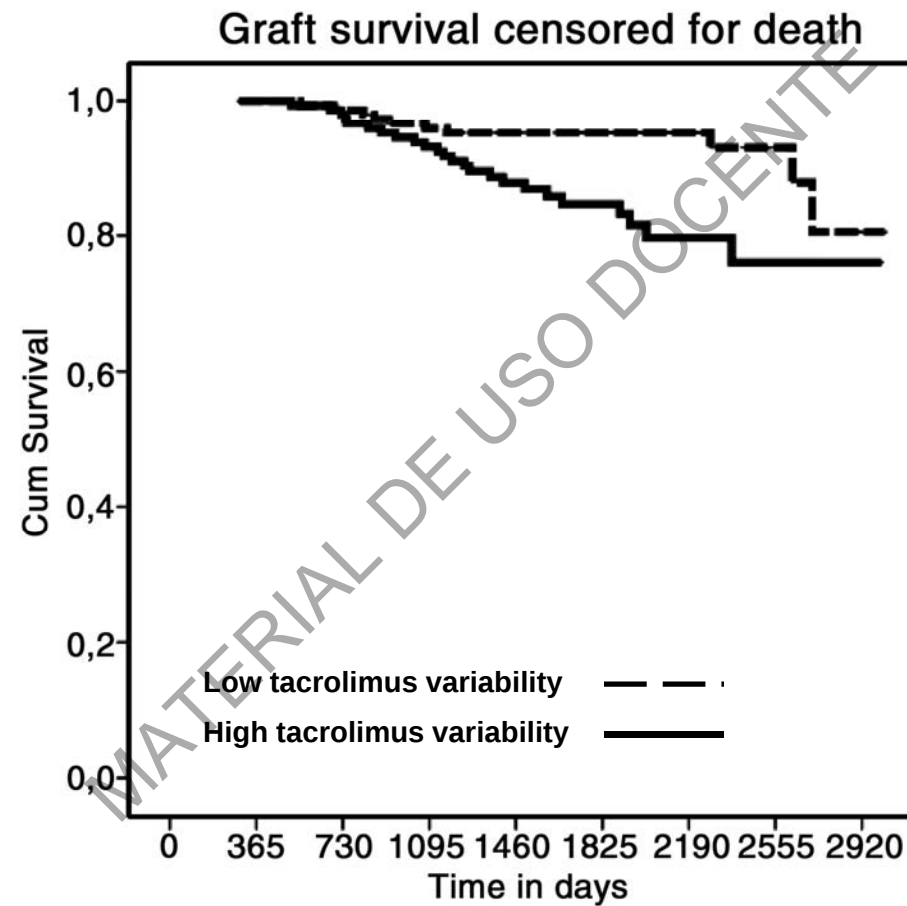
Relationship between the presence of *de novo* DSA and no DSA in graft survival
(*dnDSA* (15%) at a mean of 4.6 ± 3.0 years post-transplant)



Meta-analysis of the impact of nonadherence on graft survival



High within-patient variability in the clearance of tacrolimus is a risk factor for poor long-term outcome after kidney transplantation



¿Cómo prevenir el rechazo crónico?

1. Asegurar una exposición adecuada a los CNI
2. Monitorización inmunológica mediante biopsias y DSA
 - En pacientes hiperinmunizados?
 - Para minimización o abolición de CNI?
 - Siempre?
3. Prevenir la no-adherencia



MUCHAS GRACIAS!