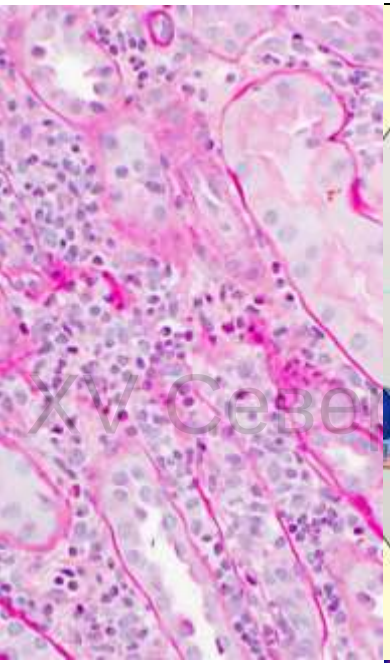
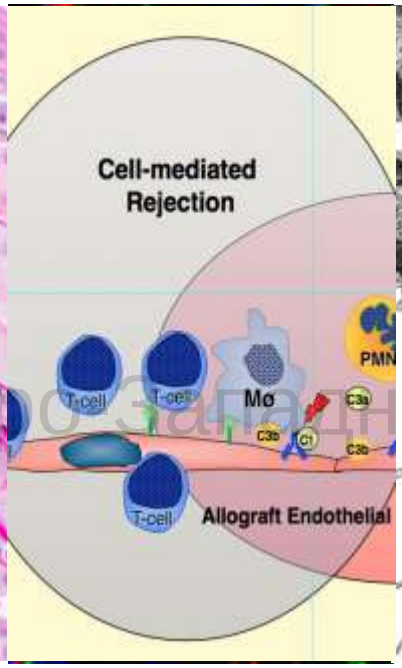
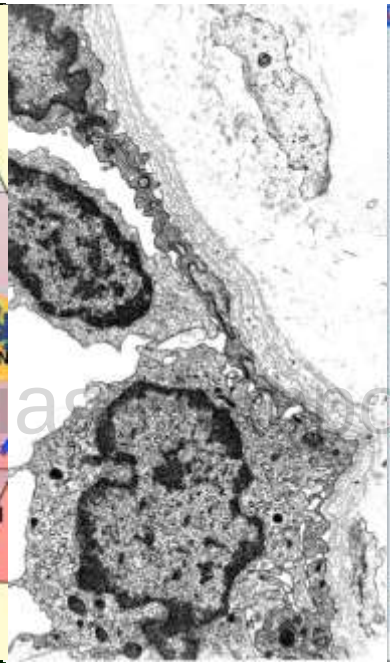
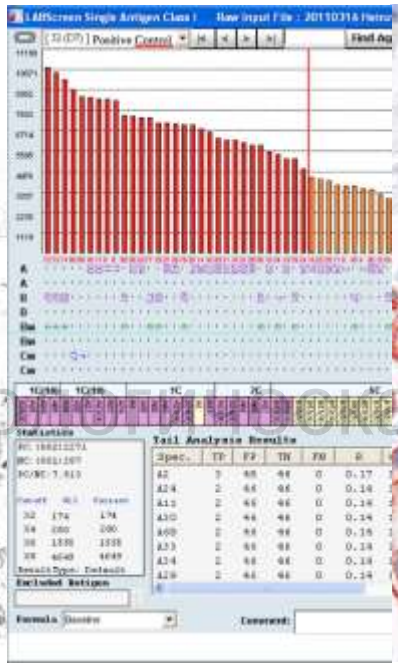
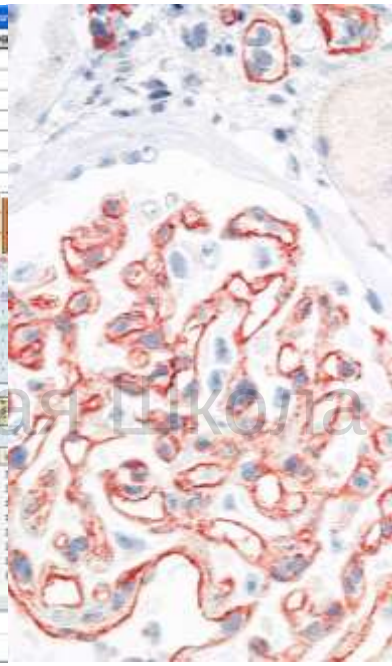
How many allograft biopsies do we need?











Heinz Regele
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UNIVERSITY
OF VIENNA

Diagnostic strategy in renal transplantation

How many biopsies do we need?

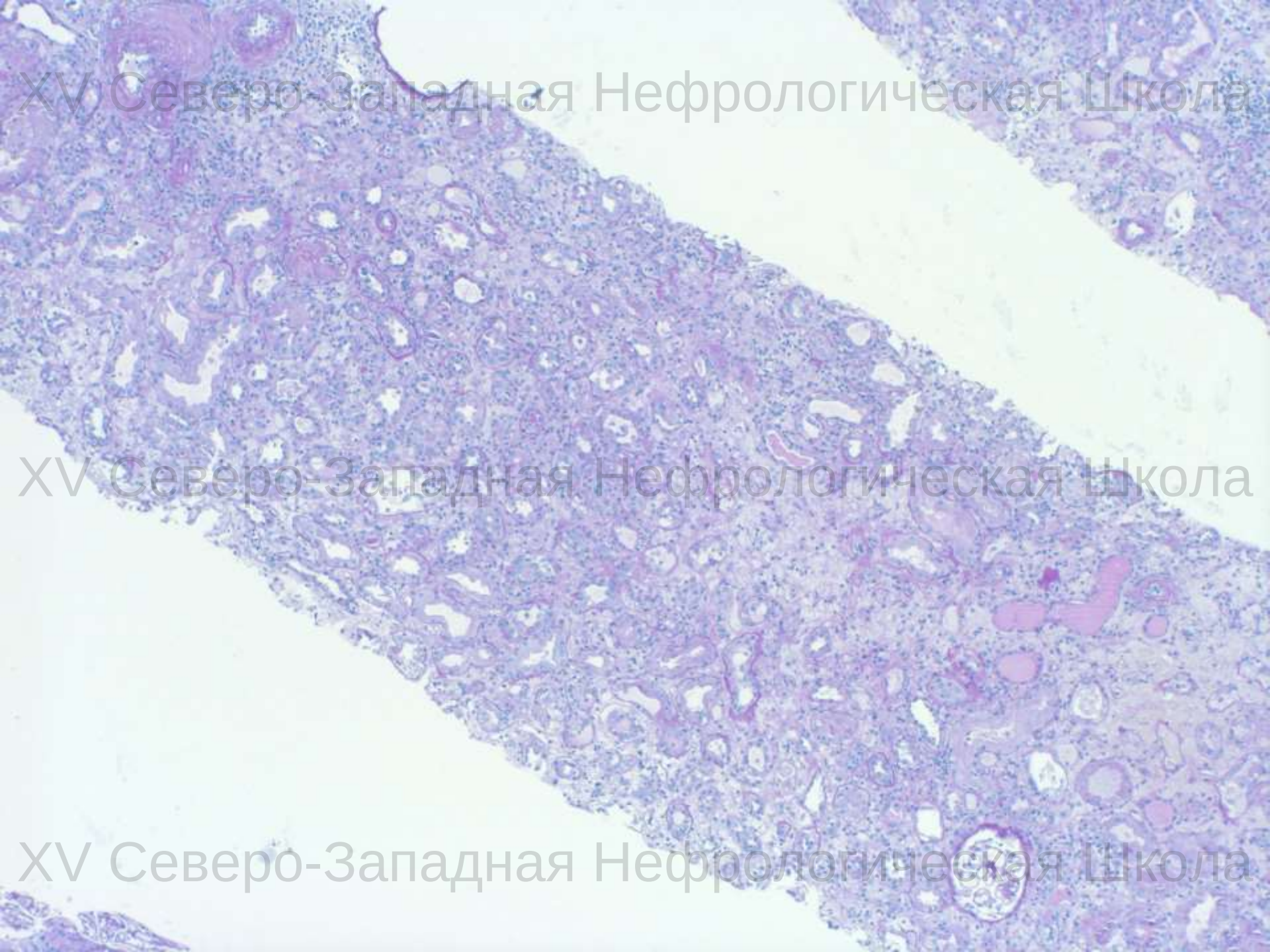
What‘s the best timing for biopsies?

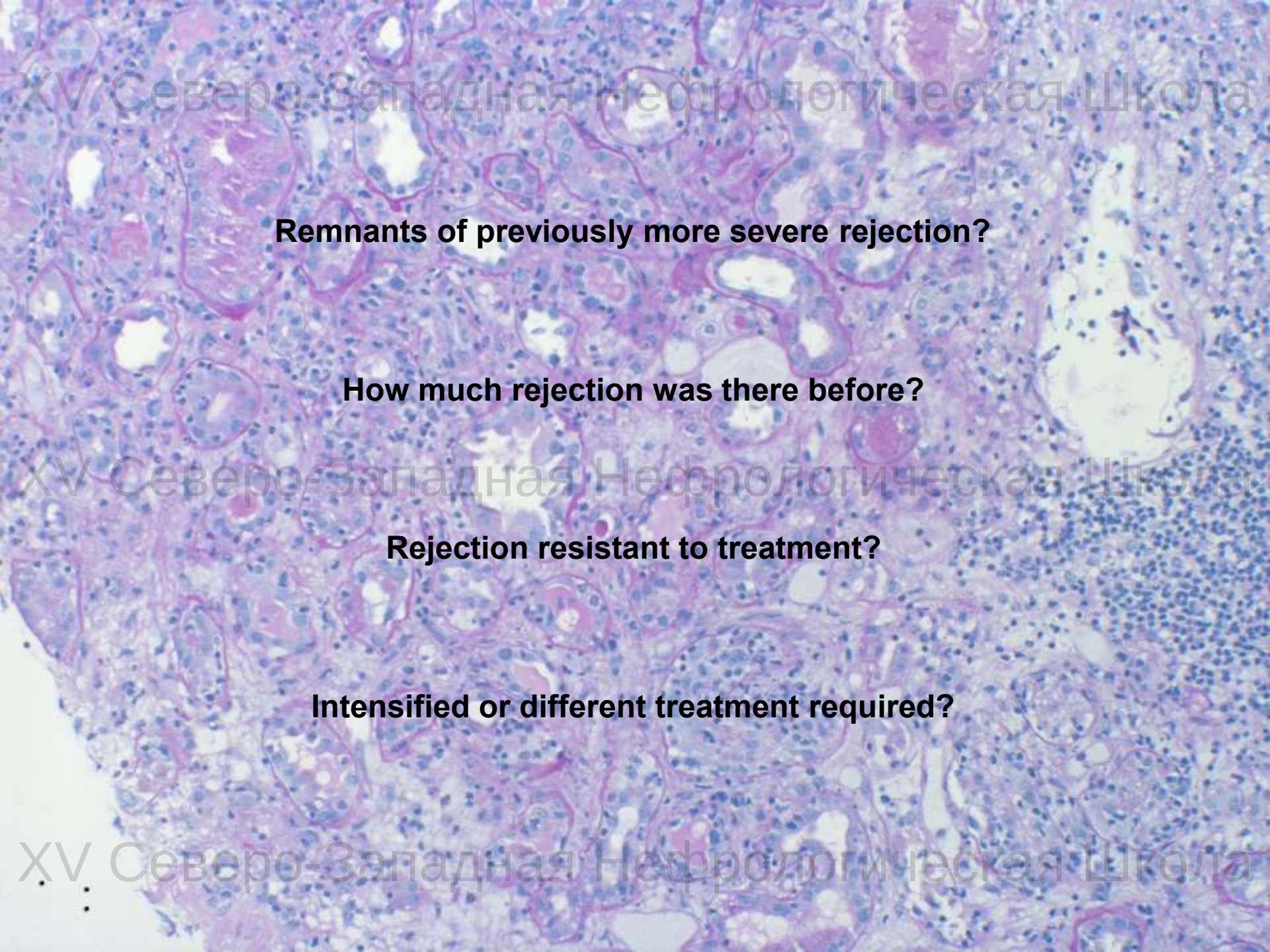
Are biopsies for cause sufficient or do we need protocol biopsies?

What's the right timing for an allograft biopsy?

As early as possible! At onset of allograft dysfunction

Avoid performing biopsies after treatment of clinically suspected rejection





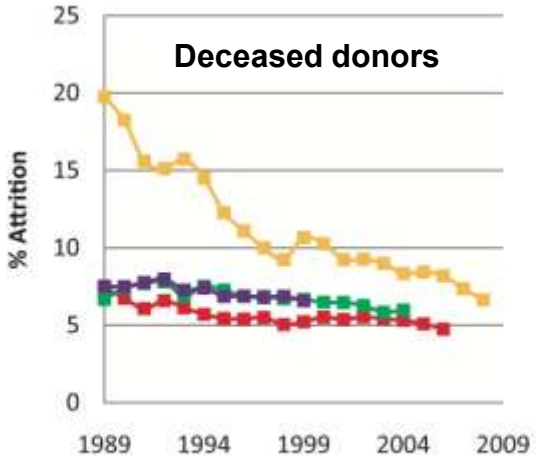
ANZDATA Registry Survival Report 2015

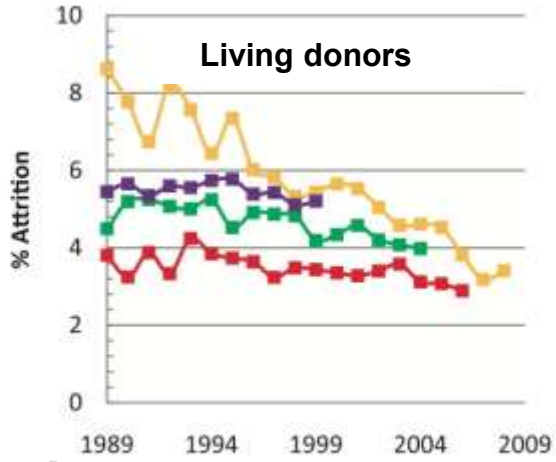
Table 8.20. Primary Deceased Donor Grafts - Australia and New Zealand 1985-2014

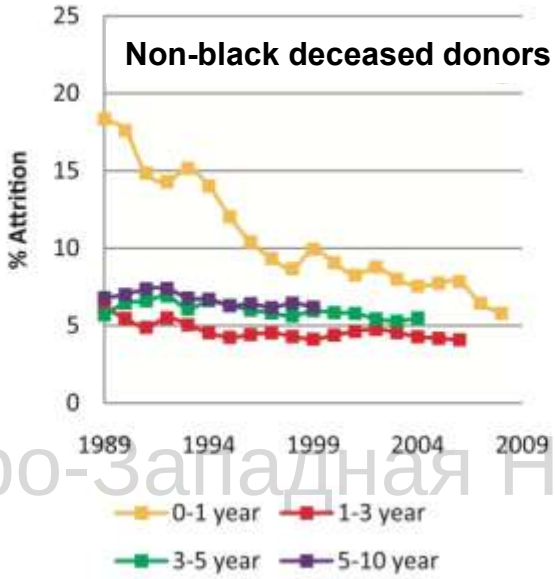
Outcome	Era	1 year	5 years	10 years	15 years	20 years
Patient survival	1985-1989 (n=1916)	92 (91, 93)	80 (78, 82)	65 (62, 67)	51 (49, 53)	40 (37, 42)
	1990-1994 (n=1906)	93 (92, 94)	84 (82, 85)	68 (66, 70)	53 (51, 55)	41 (39, 43)
	1995-1999 (n=1779)	95 (94, 96)	86 (84, 88)	72 (70, 74)	57 (55, 59)	-
	2000-2004 (n=1849)	96 (95, 97)	89 (88, 90)	77 (75, 79)	-	-
	2005-2009 (n=1911)	97 (96, 97)	90 (88, 91)	-	-	-
	2010-2014 (n=2922)	98 (97, 98)	-	-	-	-
Graft survival	1985-1989 (n=1916)	81 (79, 83)	66 (64, 68)	47 (45, 49)	33 (31, 35)	21 (20, 23)
	1990-1994 (n=1906)	85 (83, 87)	71 (69, 73)	51 (48, 53)	35 (33, 37)	23 (22, 25)
	1995-1999 (n=1779)	89 (87, 90)	76 (74, 78)	59 (56, 61)	42 (39, 44)	-
	2000-2004 (n=1849)	92 (90, 93)	81 (79, 83)	65 (62, 67)	-	-
	2005-2009 (n=1911)	92 (91, 93)	81 (79, 83)	-	-	-
	2010-2014 (n=2922)	95 (94, 96)	-	-	-	-

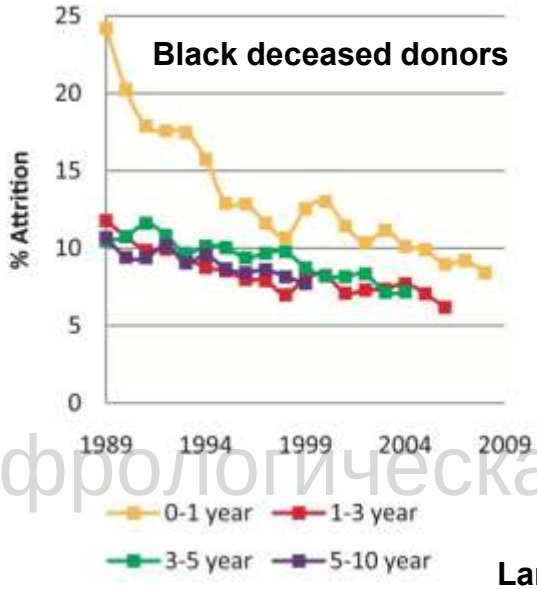
Graft loss rates

SRT (Scientific Renal Transplant) Registry data on 252910 renal transplants 1989-2005





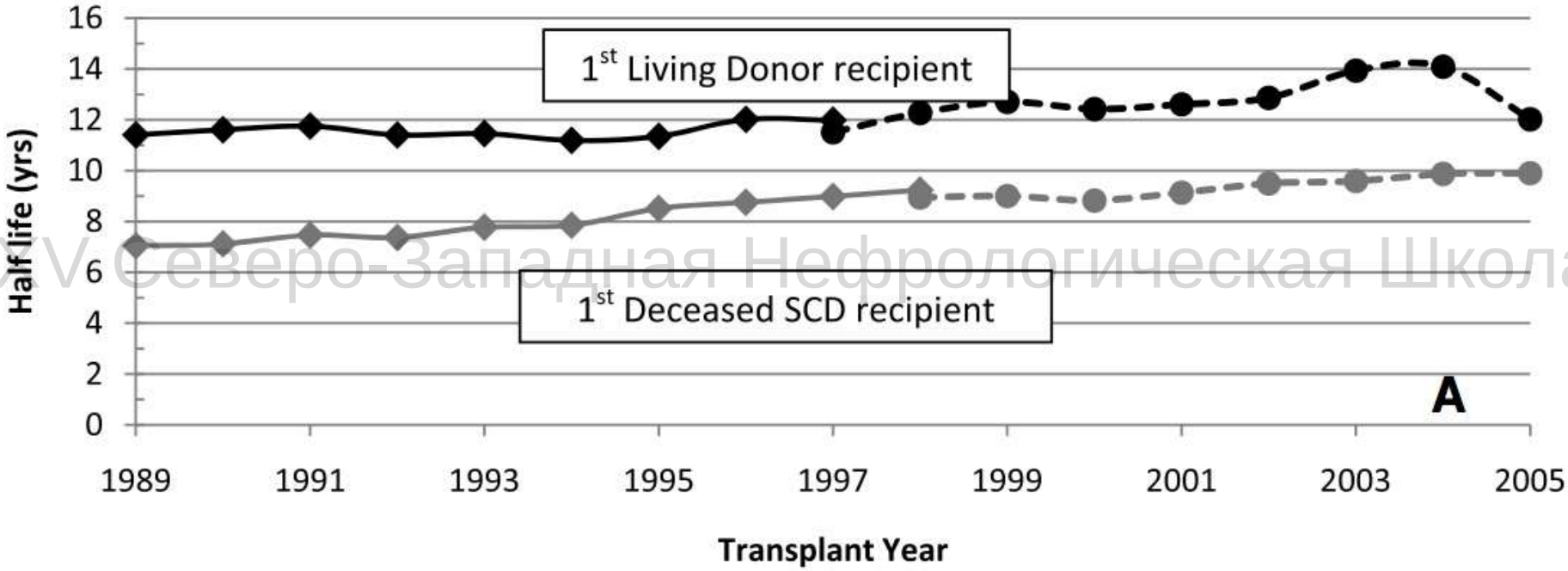




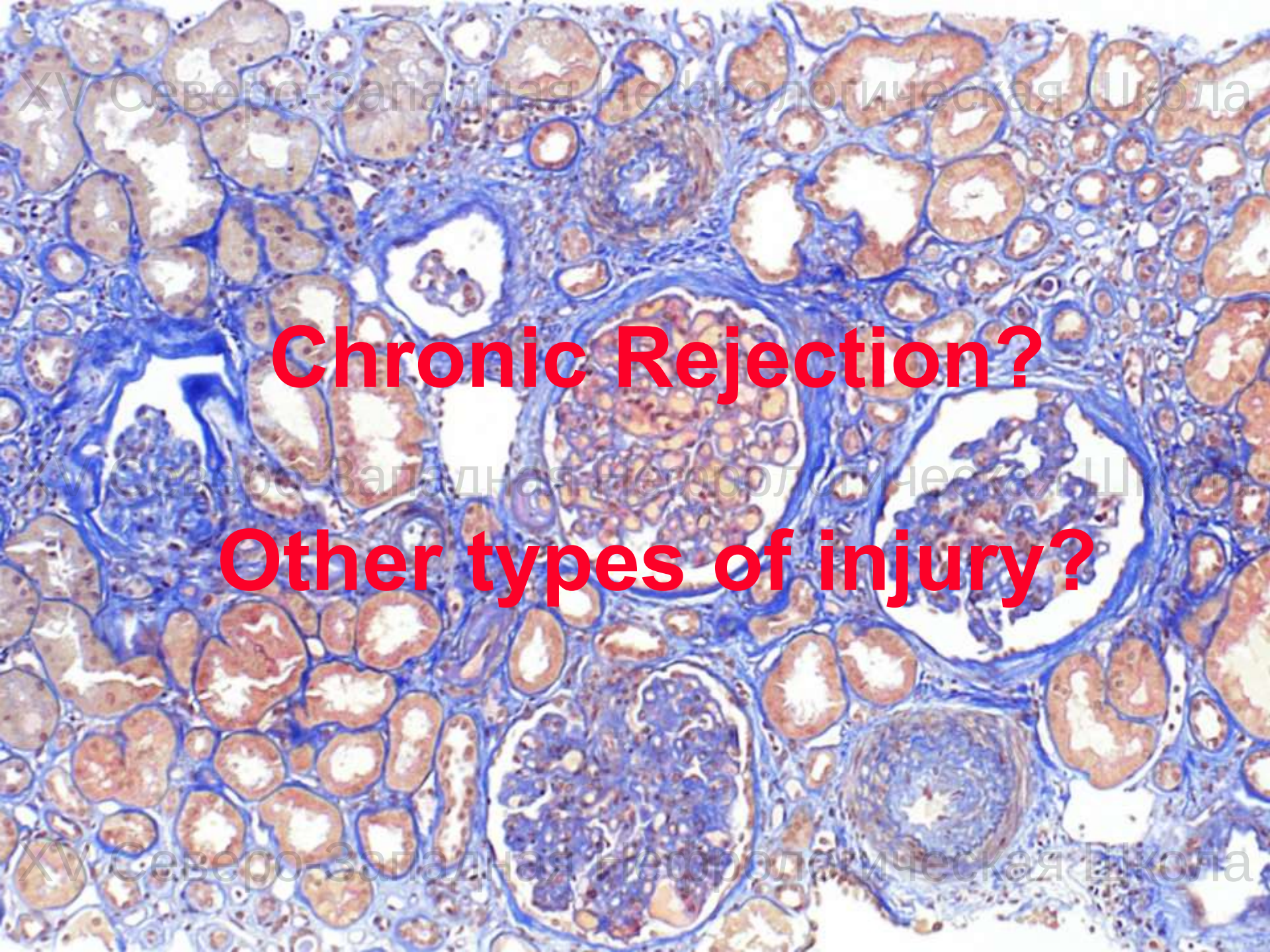
Lamb K.E. et al., AJT 2011

Long Term Renal Allograft Survival

SRT-registry data on 252910 renal transplants 1989-2005

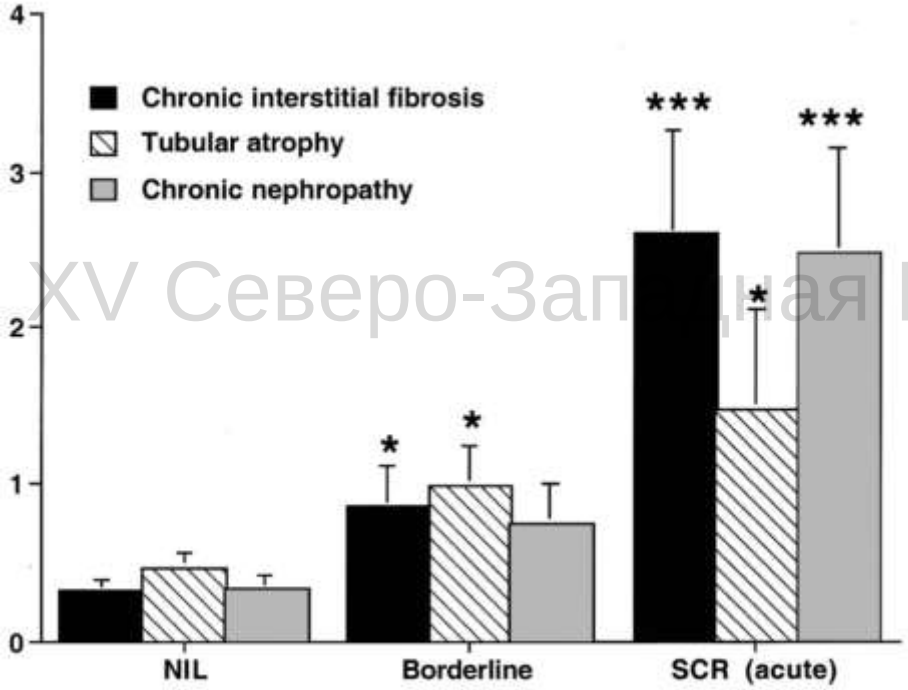


Lamb K.E. et al., AJT 2011



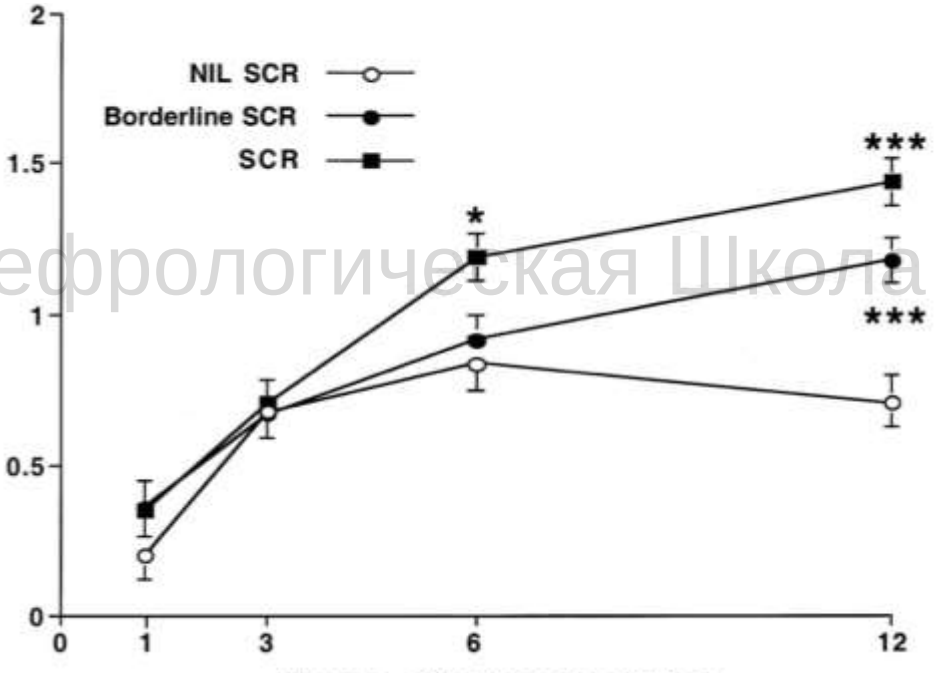
Subclinical rejection (SCR) precedes interstitial fibrosis

Differential Banff Scores



Preceeding biospsy

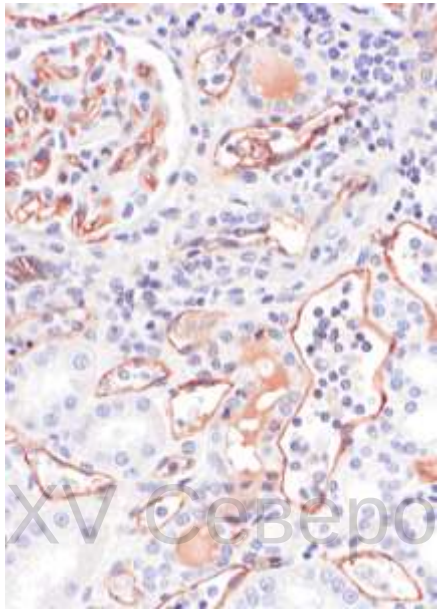
Chronic interstitial fibrosis score

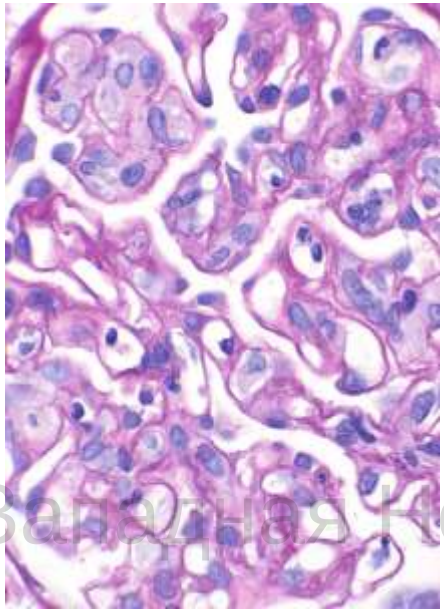


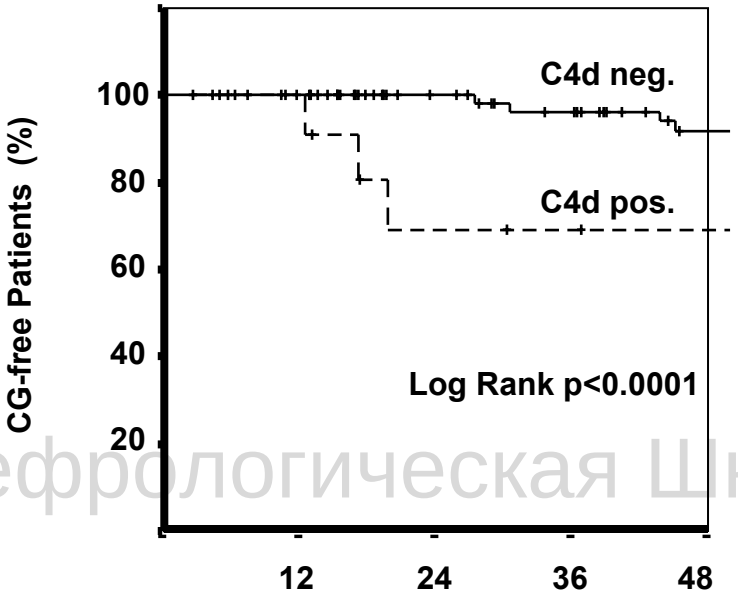
Months after transplantation

Nankivell et al., Transplantation 2004

Acute microvascular injury precedes chronic TX-glomerulopathy (cg) and is associated with accelerated graft loss







Patients at risk					
C4d neg.	83	75	58	38	26
C4d pos.	13	11	6	5	4

Regele et al., JASN 2002

C4d in peritubular capillaries was associated with HLA Class II antibodies and was an independent risk factor for graft failure after TG diagnosis.

Issa et al., Transplantation 2008

Pathogenesis of allograft loss

The Three Element Concept

Disease or condition

- ***Rejection***
  - ***TCMR*** ***ABMR***
  - ***Non-adherence***
- ***Other diseases and conditions***
  - e.g. brain death, implantation
  - viruses, primary diseases, drug toxicity

The injury-repair response

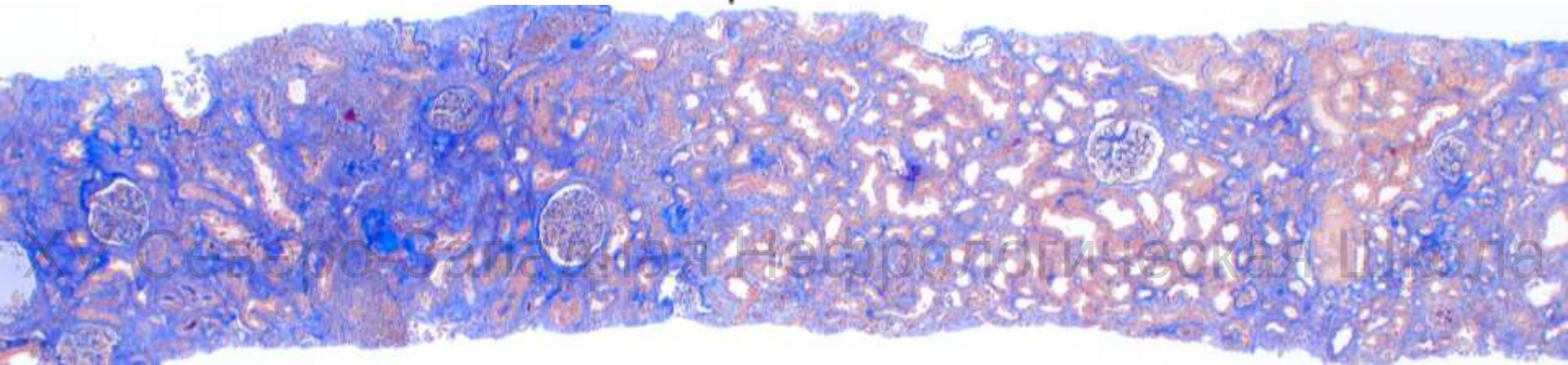
Active injury-repair response

Parenchyma:
- injury-up: developmental pathways, cell cycle, apoptosis;
- injury-down: dedifferentiation, loss of function molecules

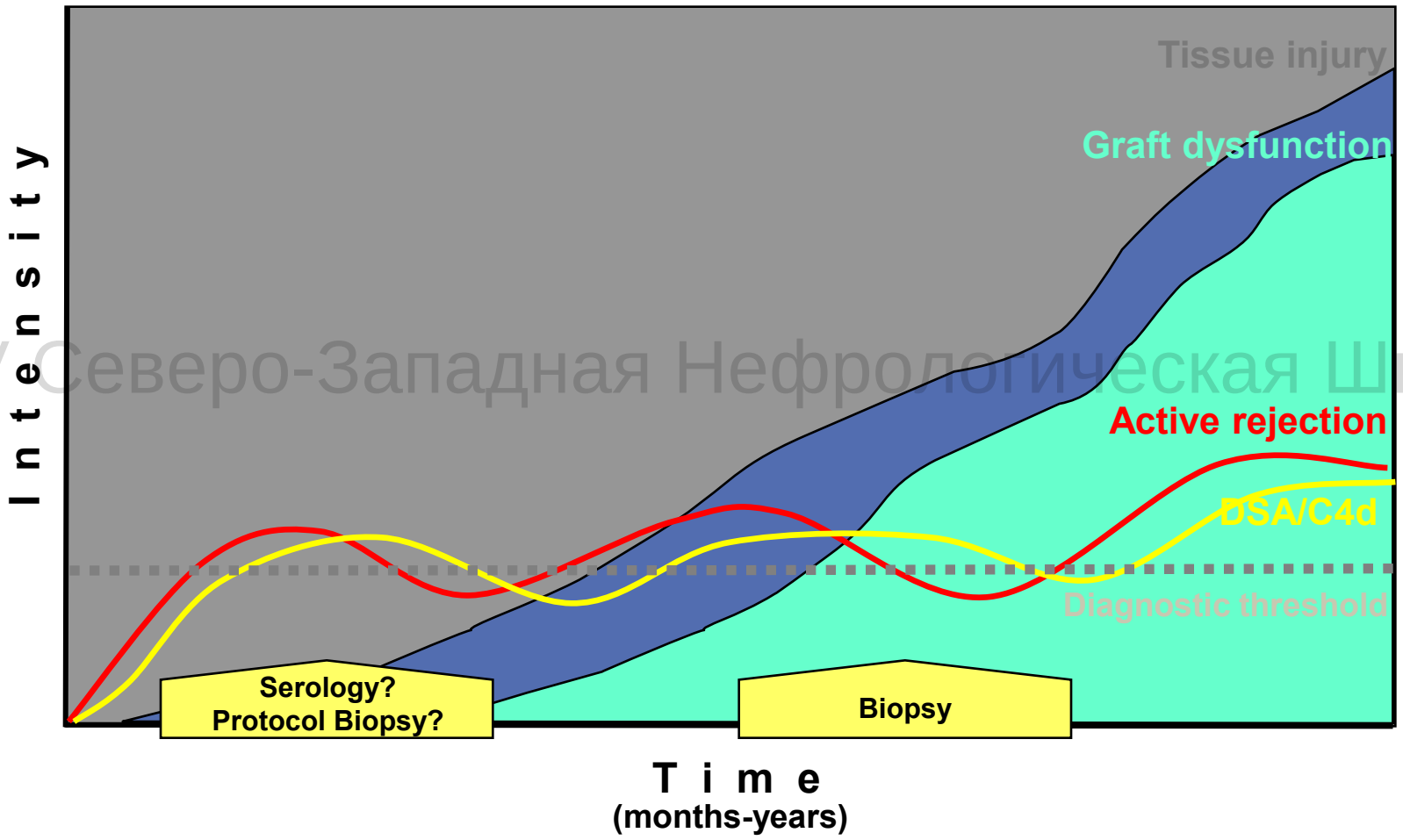
Stroma and microcirculation changes

Secondary inflammation: macrophages; T cells

If repair of injury fails



Development of chronic allograft injury



Prevention of chronic allograft injury

Perform protocol biopsy

↓

Treat subclinical rejection

↓

Prevent chronic rejection and graft fibrosis!

XV Северо-Западная Нефрологическая Школа

Overall prevalence of subclinical rejection was 4.6%. Creatinine clearance at 6 months was 72.9 +/- 21.7 in the Biopsy and 68.90 mL/min +/- 18.35 mL/min in the Control arm patients (p = 0.18). In conclusion, **we found no benefit to the procurement of early protocol biopsies in renal transplant patients receiving TAC, MMF and prednisone, at least in the short term**. This is likely due to their low prevalence of subclinical rejection.

Rush D et al, Am J Transplant 2007

SCR in early protocol biopsies (d7 and d28) is rare (5,4 %). Untreated borderline changes did not have an adverse impact on graft function at 1 year post-transplantation. New immunosuppressive regimens may reduce subclinical in addition to clinical rejection-frequency, suggesting that the relative benefit of early protocol biopsies in detecting SCR is also reduced.

Roberts IS et al, Transpl Internat 2009

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

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

Robert S. Gaston,[1,11] J. Michael Cecka,[2] Bert L. Kasiske,[3] Ann M. Fieberg,[4] Robert Leduc,[4] Fernando C. Cosio,[5] Sita Gourishankar,[6] Joseph Grande,[9] Philip Halloran,[6] Lawrence Hunsicker,[7] Roslyn Mannon,[1] David Rush,[8] and Arthur J. Matas[10]

Transplantation. 2010 Jul 15;90(1):68-74

DSA in stably functioning grafts

164 recipients with >1year graft function
1 year serial HLA Ab monitoring
Follow-up: median 69 months

Separate analysis of patients with excellent 1y graft function

1. GFR ≥60 ml/min

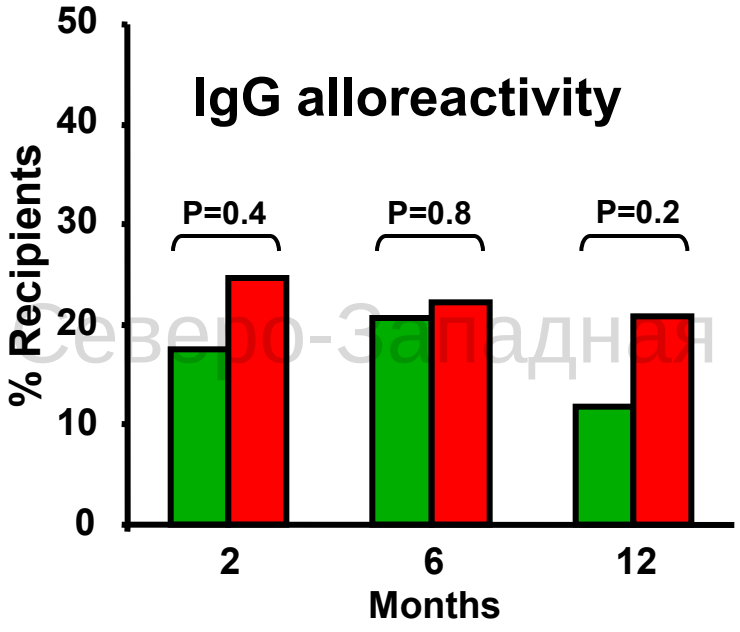
2. 24h protein excretion ≤0.5 g

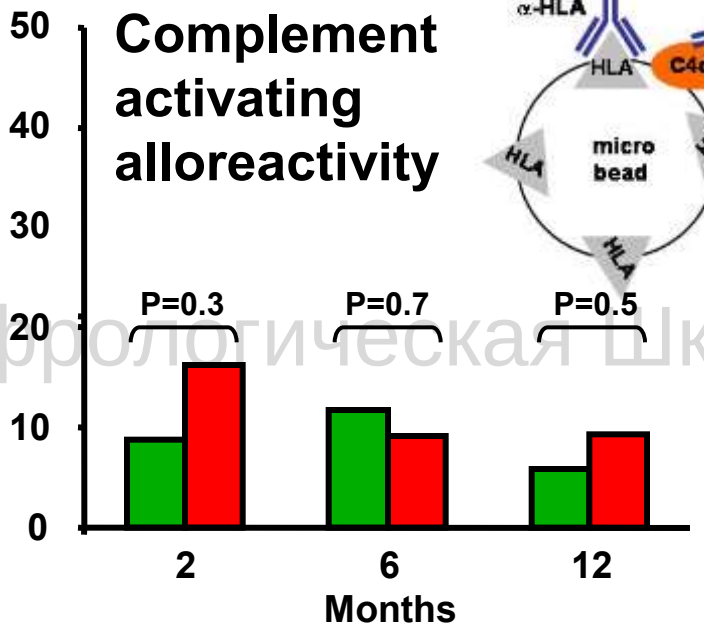
3. No dysfunction/indication biopsy

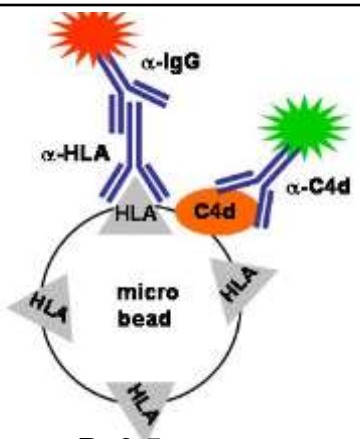
4. No desensitization or rejection treatment

Bartel et al, Am J Transplant 2008

IgG HLA Ab in renal Tx recipients with excellent 1 year course







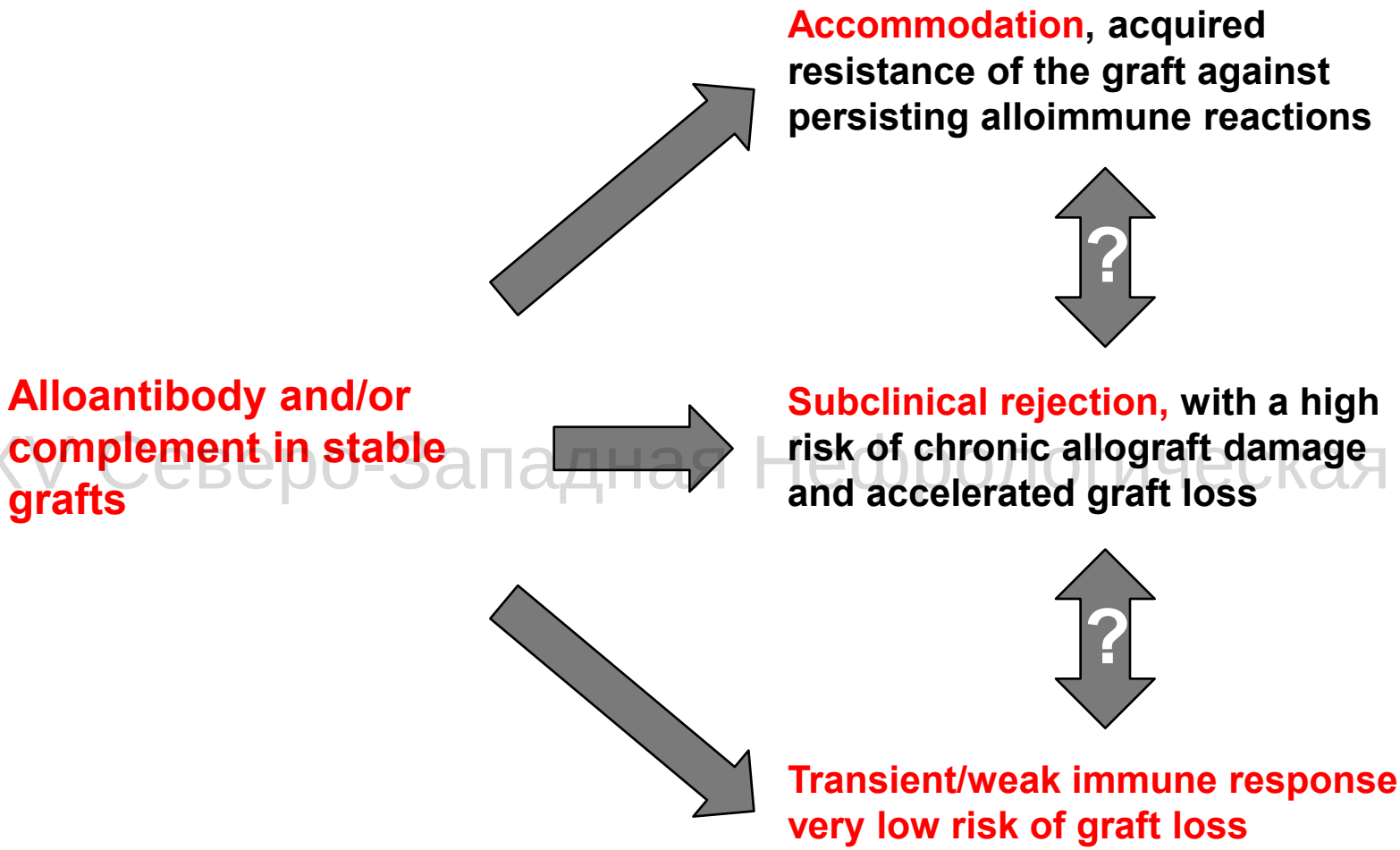
Excellent function during 1st year (n= 34)

Dysfunction during 1st year (n=130)

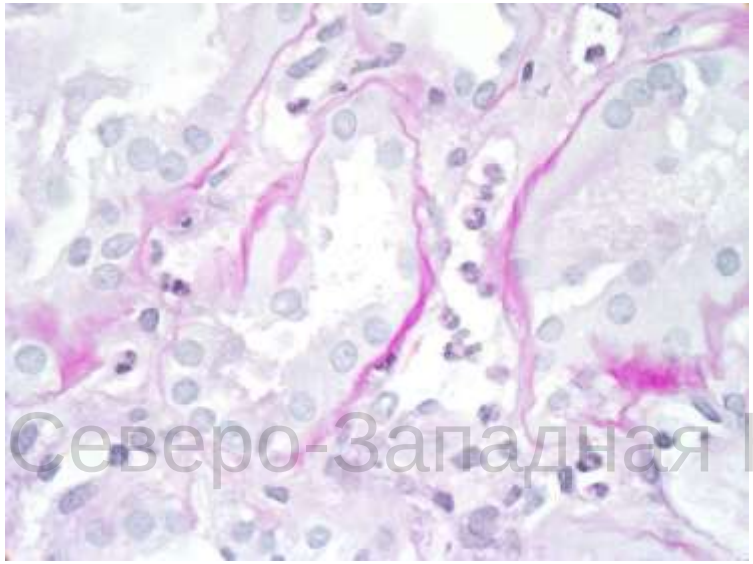
No difference to non-stable patients

- ✔ Incidence
- ✔ Binding strength
- ✔ DSA frequency
- ✔ C4d-fixation in vitro

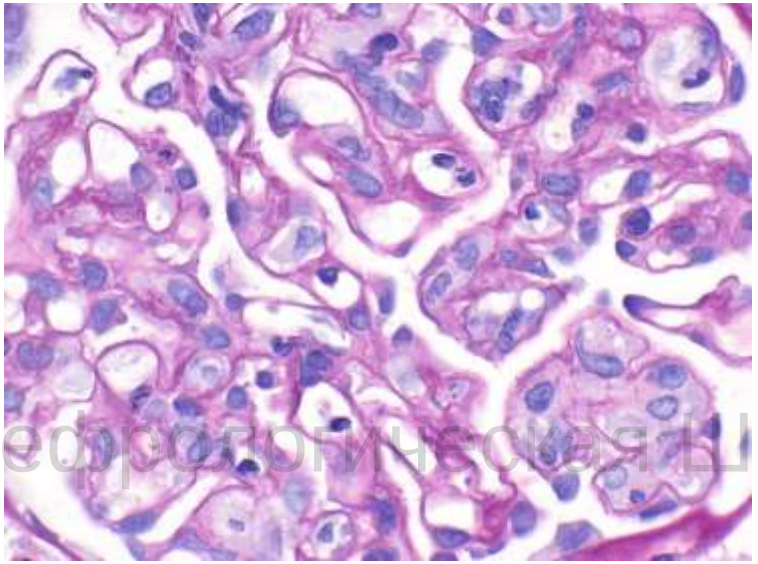
Bartel et al, Am J Transplant 2008



Microvascular injury and chronic rejection



Peritubular capillaritis



Glomerulitis

In protocol biopsies, PTCitis at 3 months was associated with chronic antibody mediated rejection at 12 months.

E. Lerut et al., Transplantation 2007

10/10 recipients with subclincal AMR showed accumulation of immune cells in peritubular capillaries (PTCitis) and 8/10 had glomerulitis.
Subclinical AMR is associated with increase of cg, ci and ct in follow up Bx.

M. Haas et al., AJT 2006

Protocol/surveillance biopsies for monitoring allografts

PROS	CONS
Biopsy provides direct access to the graft	Painful, potentially harmful with serious complications in 0,5-1%
Can detect active/ongoing graft injury before it becomes clinically apparent	SCR is very rare (<5%) under modern immunosuppression
Helps in identifying early stages of chronic fibrotic tissue damage	Procurement and processing of biopsies is time consuming and costly
Histopathology is still the gold standard for assessing alloimmunity	Biopsy diagnostics has inherent limitations like sampling error, lack of specificity….

Surveillance biopsy? If yes, when?

Donor kidneys biopsy

- Determines the baseline condition of the graft
- Detects donor transmitted disease (TMA, GN, malignancy....)
- Helps in assessing donor organ quality before TX

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Histological scoring of donor organ quality

Table 1. Summary of some commonly used scores in the assessment of donor biopsies

Name (year published)	Variables scored		Predictive value	Reference
Banff schemebased scores	Variables	Points	(a) AUC: 0.79 [29]	(a): [18,22]
(a) Remuzzi (1999)	Global glomerulosclerosis (a–c)	0–3	(b) AUC: 0.76 [29]	(b): [60]
(b) CADI (1994)	Interstitial fibrosis, ci (a–c)	0–3	(c) AUC: 0.74	(c): [56]
(c) Total chronic Banff (2008)	Tubular atrophy, ct (a–c)	0–3		
	Vessel narrowing, cv (a–c)	0–3		
	Mesangial matrix increase, mm (b–c)	0–3		
	Interstitial inflammation, i (b)	0–3		
	Glomerular double contour, cg (c)	0–3		
	Arteriolar hyalinosis, ah (c)	0–3		
Maryland Aggregate Pathology Index (2008)	Variables	Points	AUC: 0.70–0.74	[30]
	Periglomerular fibrosis: present/absent	4		
	Arteriolar hyalinosis: present/absent	4		
	Scar (focus of sclerosis and IFTA ≥10 tubules: present/absent)	3		
	Global glomerulosclerosis ≥15%	2		
	Wall-lumen ratio of interlobular arteries ≥0.5	2		
		5-year graft survival		
	Low risk group (score sum: 0–7)	90%		
	Intermediate risk group (score sum: 8–11)	63%		
	High risk group (score sum: 12–15)	53%		
French clinico-histopathological composite score (2008)	Variables:	Points	AUC: 0.84	[29]
	Global glomerulosclerosis ≥10% (GS)	1		
	Donor hypertension and/or donor serum creatinine ≥150 μmol/l (CP)	1		
		eGFR <25 ml/min at 1 year		
	GS = 0 and CP = 0	5.2%		
	GS = 1 and CP = 0	12.5%		
	GS = 0 and CP = 1	13.5%		
	GS = 1 and CP = 1	35.1%		

Hopfer H et al, Curr Opin Organ Transplant 2013

Surveillance biopsy? If yes, when?

Donor kidneys biopsy

- Determines the baseline condition of the graft
- Detects donor transmitted disease (TMA, GN, malignancy....)
- Helps in assessing donor organ quality before TX

Risk adjusted surveillance biopsies:

Biopsies in patients at risk of rejection (or other potentially subclinical disease)

- Sensitised patients (ABO incompatible, anti-HLA)
- De-novo DSA
- Suspicion of non-adherence
- Reduced immunosuppression (per protocol, Polyoma, malignancy....)

Summary

Histological assessment of renal allograft biopsies still is the gold standard for detection and classification of transplant rejection

Donor kidney biopsies can provide crucial information about pre-existing tissue injury and might also help to assess donor kidney quality prior to transplantation

Rejection and other types of injury are dynamic processes and may be focally accentuated and might therefore require sequential (surveillance) biopsies for proper assessment

Timing of surveillance biopsies should be specifically adjusted to the patients' risk profile

Therefore

Whenever you think it might be useful to know what's going on in a kidney transplant

Perform a biopsy!