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Disclosure.

- Dr Mark Stegall.
- Institution : Mayo Clinic, Rochester.
- Research contracts with Alexion and Millennium
- My presentation includes discussion of off-label and investigational.
- Yes—Eculizumab, Alexion Pharmaceuticals;

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Antibody Mediated Rejection

Mark D Stegall MD
Professor of Surgery and Immunology

*

asterisk

Center-specific outcome
Observed lower than expected

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Antibody Mediated Rejection
Three Clinical Settings

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Antibody Mediated Rejection
Three Clinical Settings

- Acute antibody mediated rejection early after transplantation→ sensitized patient

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- Chronic antibody “associated” injury→?may be due to several “causes”

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Antibody Mediated Rejection
Three Clinical Settings

- Acute antibody mediated rejection early after transplantation→ sensitized patient

Treatable

- Combined acute cellular and humoral rejection→poor compliance
- Chronic antibody "associated" injury→?may be due to several "causes"

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EarlyAMR

- "Perfect Match"/0-ABDR, DQ mismatch kidney offered to 50 y/o woman 99% cPRA (KDPI 10%)
- Crossmatch: T cell FXM negative/B FXM 213
- Do the transplant (Saturday night)

Monday: Post Op Day 2

- Transplant is doing great

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- Transplant is doing great
- Tissue Typing Lab calls

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Monday: Post Op Day 2

- Transplant is doing great
- Tissue Typing Lab calls
- Donor DPB1*0301,1401
- Recipient DPB1*0401,0402
- Pre-Txplant antibody: anti-DP01, 03,05,11 (MFI 5400)

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Sunday: Post Op Day 6

- Creatinine 0.6→1.5
- Ultrasound—normal, ?ATN
- Prograf 12.2 ng/dl

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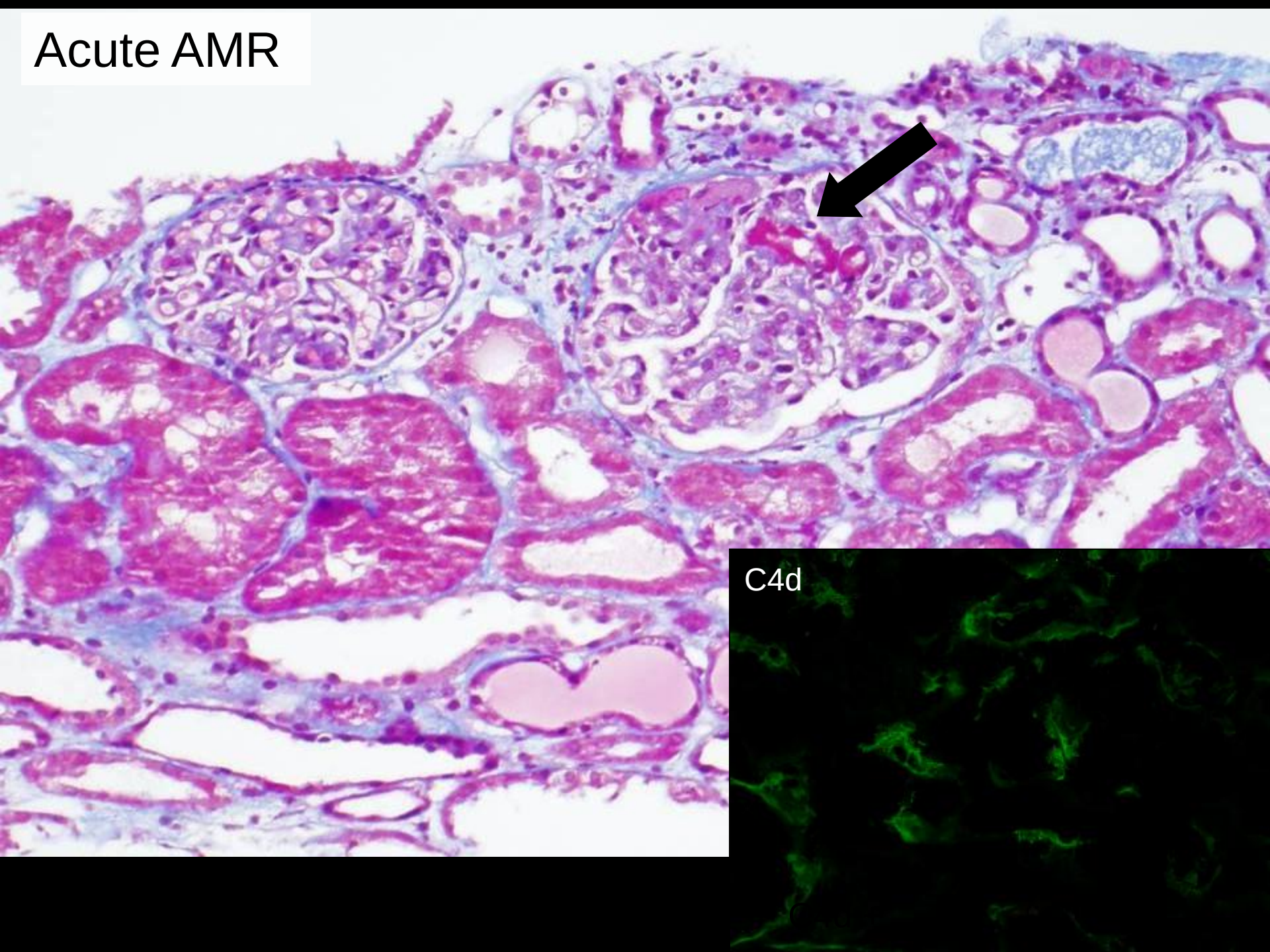
Monday: Post Op Day 7

- Creatine 2.7 mg/dl
- Low urine output
- Biopsy, single antigen beads ordered

Biopsy

- Acute AMR
- Glomerular microthrombi, ATN, C4d+,

Acute AMR



What to do?

- Plasma exchange
- Daily until creatinine improves

DP 03 MFI = 12,300 (Tuesday)

American Journal of Transplantation 2008; 8: 2684–2694
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2008.02441.x

Alloantibody Levels and Acute Humoral Rejection Early Aft

J. M. Burns[a], L.
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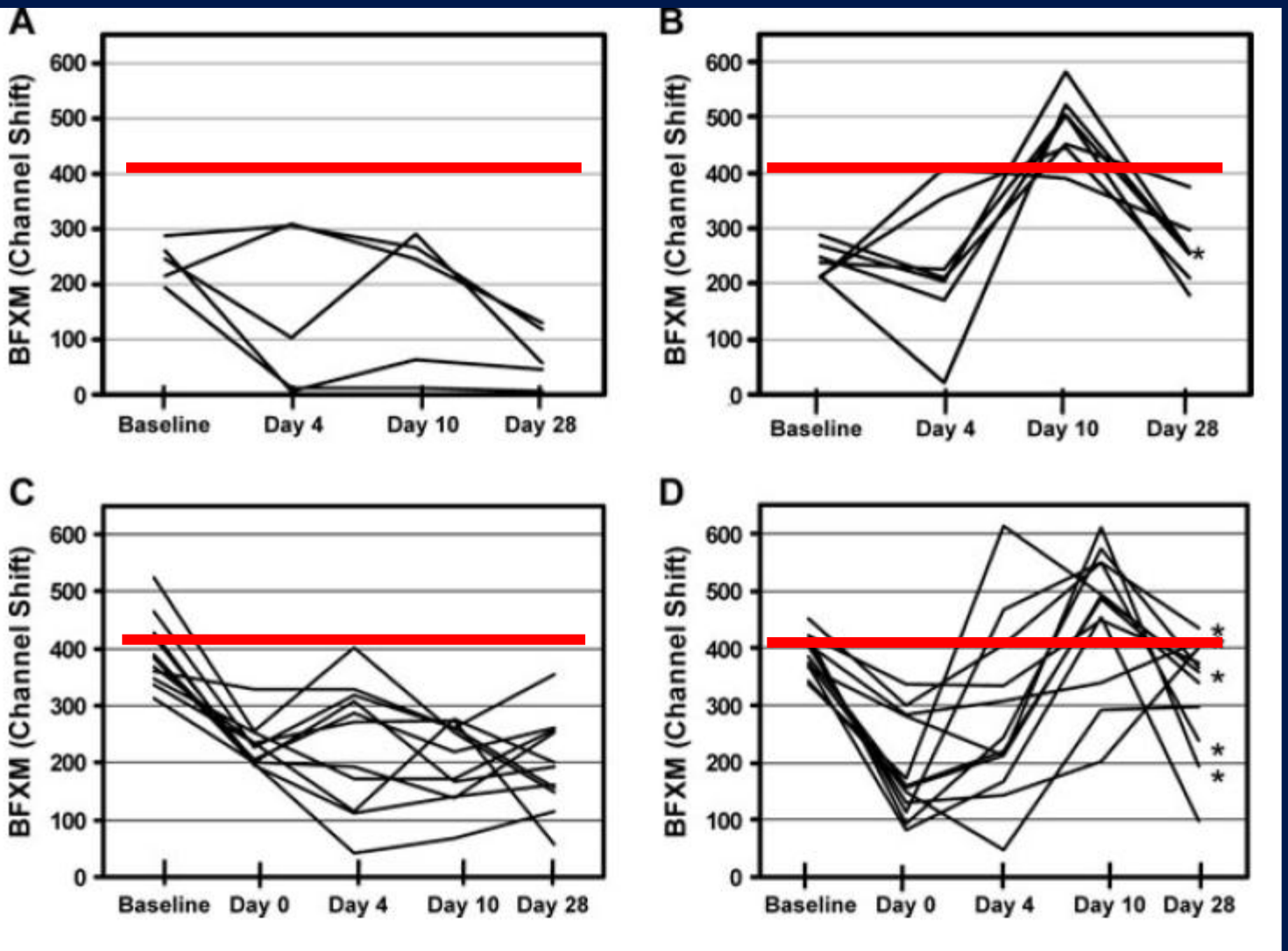
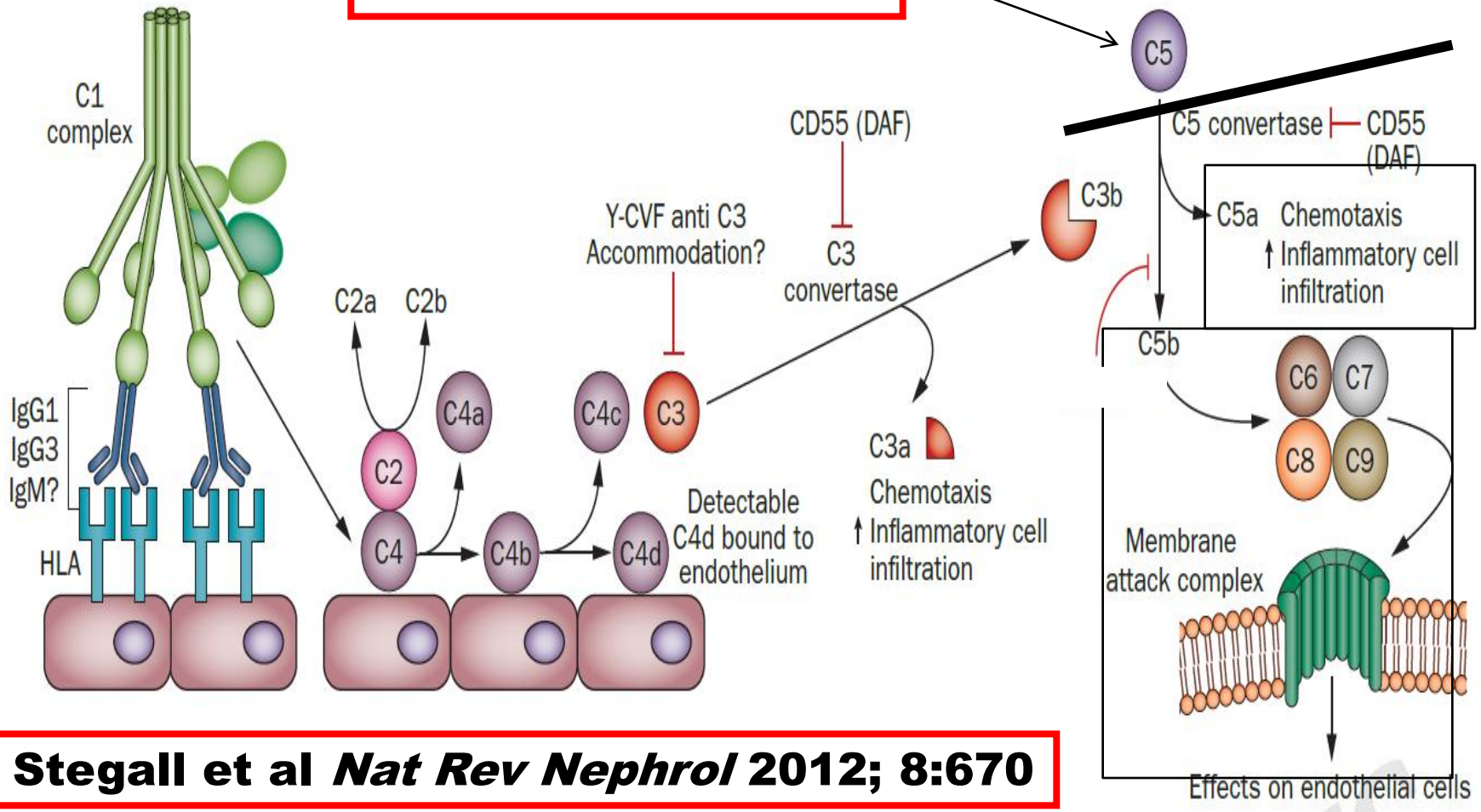
M. J. Gandhi[b], F

[a]Division of Transp
[b]Department of La
[c]Division of Nephr
Internal Medicine a



Complement-Mediated Antibody Damage

Eculizumab
Anti-C5 ab



Stegall et al *Nat Rev Nephrol* 2012; 8:670

American Journal of Transplantation 2011; 11: 2405–2413
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2011.03757.x

Terminal Complement Inhibition Decreases Antibody-Mediated Rejection in Sensitized Renal Transplant Recipients

M. D. Stegall[a,*], T. Diwan[a], S. Raghavaiah[a], L. D. Cornell[b], J. Burns[a,c], P. G. Dean[a], F. G. Cosio[d], M. J. Gandhi[b], W. Kremers[e] and J. M. Gloor[d]

[a] *William J. von Liebig Transplant Center, Division of Transplantation Surgery, Mayo Clinic, Rochester, MN*
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Key words: Alloantibodies, anti-HLA antibodies, antibody-mediated rejection, complement, chronic rejection, kidney transplantation, sensitized recipients

Abbreviations: AMR, antibody-mediated rejection; BFXM, B-cell flow cytometric crossmatch; DSA, donor-specific alloantibody; HLA, human leukocyte antigens; PE, plasma exchange.

Received 01 March 2011, revised 31 May 2011 and accepted for publication 01 June 2011

Results

Category	Eculizumab Group (n=26)	Control Group (n=51)	p value
Follow-up (mean months ± SD, range)	11.9 ± 6.1 (3.0 – 27.5)	48.8 ± 14.1 (7.8 – 69.8)	
Graft Survival at 1 year (n, %)	16/16 (100%)	49/51 (97%)	1.00
Acute antibody mediated rejection ≤ 3months (n, %)	2 (7.7%)	21 (41%)	0.0031
Patients developing High DSA Levels ≤ 3 months *	13 (50%)	22 (43%)	0.63
High DSA Biopsies C4d+ (n, %)	13 (100%)	20 (90.9%)	0.52
High DSA and C4d+ biopsies Showing acute AMR (n, %)	2 (15%)	20 (100%)	<0.0001
Cellular Rejection ≤3 months (n, %)	1 (6.2%)	1 (2.0%)	0.42

What to do?

- Plasma exchange
- Daily until creatinine improves
- Eculizumab after every PE

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Need to have a protocol/algorithm to diagnose and treat early AMR

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Rare, but you will see it

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- **Combined acute cellular and humoral rejection→poor compliance**
- Chronic antibody "ass injury→?may be due to several "causes"

May be treatable

Case #2

- A different patient comes back at 9 months after transplantation
- Baseline creatinine 1.2, now 3.5
- Has not taken meds for 2 months

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Workup

- Ultrasound—normal, ?ATN
- Biopsy—Banff 2a cellular rejection, C4d weak, diffuse in peritubular capillaries, peritubular capillaritis
- Single antigen beads--4400

Celllular or Humoral or both?

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Combined Cellular and Humoral

- Treat the cellular component
- Treat the antibody component if the DSA is high (ex. >4000)

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Combined Cellular and Humoral

- Treat the cellular component
- Treat the antibody component if the DSA is high (ex. >4000)
- Prognosis

Combined Cellular and Humoral

- Treat the cellular component
- Treat the antibody component if the DSA is high (ex. >4000)
- Prognosis
  - Depends on the amount of chronic injury present the biopsy
  - Depends on persistence of DSA

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May not be treateable

Case #3

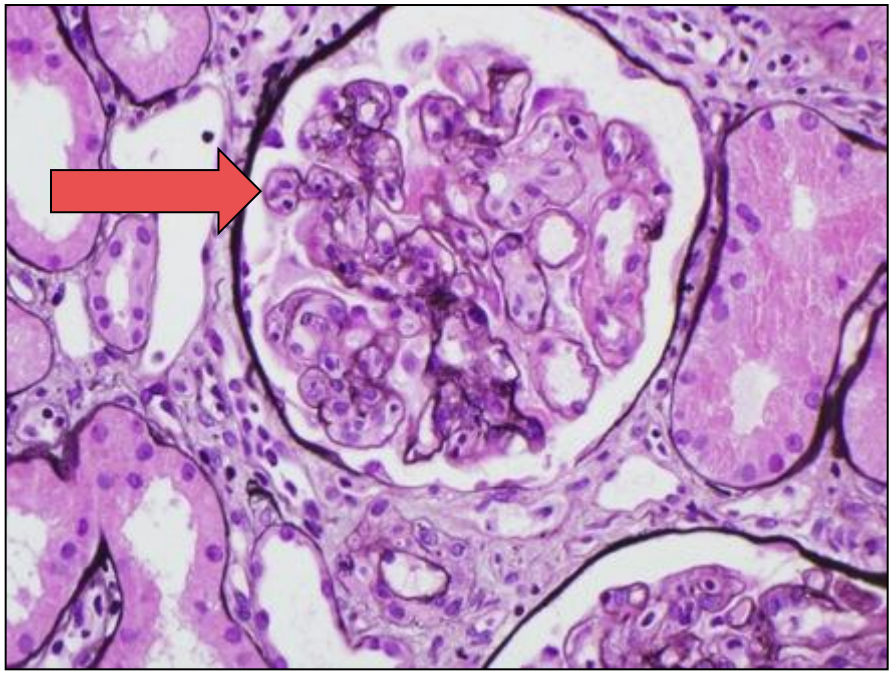
- Patient 5 years after transplantation
- Hx acute cellular rejection at 3 months
- Baseline creatinine 1.2 at 1 year—1.7 at 4 years, now 2.3 at 5 years

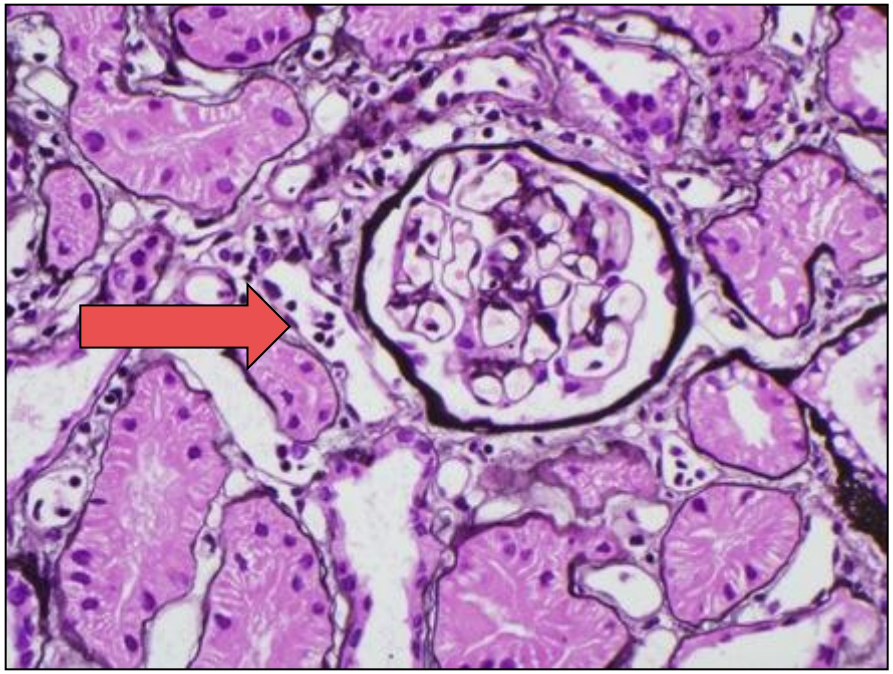
Workup

- Single antigen beads—anti-donor DR4 (MFI = 3200)
- Biopsy—chronic antibody mediated rejection (peritubular capillaritis, mild transplant glomerulopathy, C4d weakly positive)

Antibody-associated chronic histologic changes

- Transplant glomerulopathy by light microscopy
- Peritubular capillaritis (ptc ≥2)





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NK cells, T cells, Macrophages

Chronic Antibody Mediated Rejection

- Bad prognosis—4 yr graft survival ~40%

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Chronic Antibody Mediated Rejection

- Bad prognosis—4 yr graft survival ~40%
- Cause: Antibody “associated” but may also become independent of DSA

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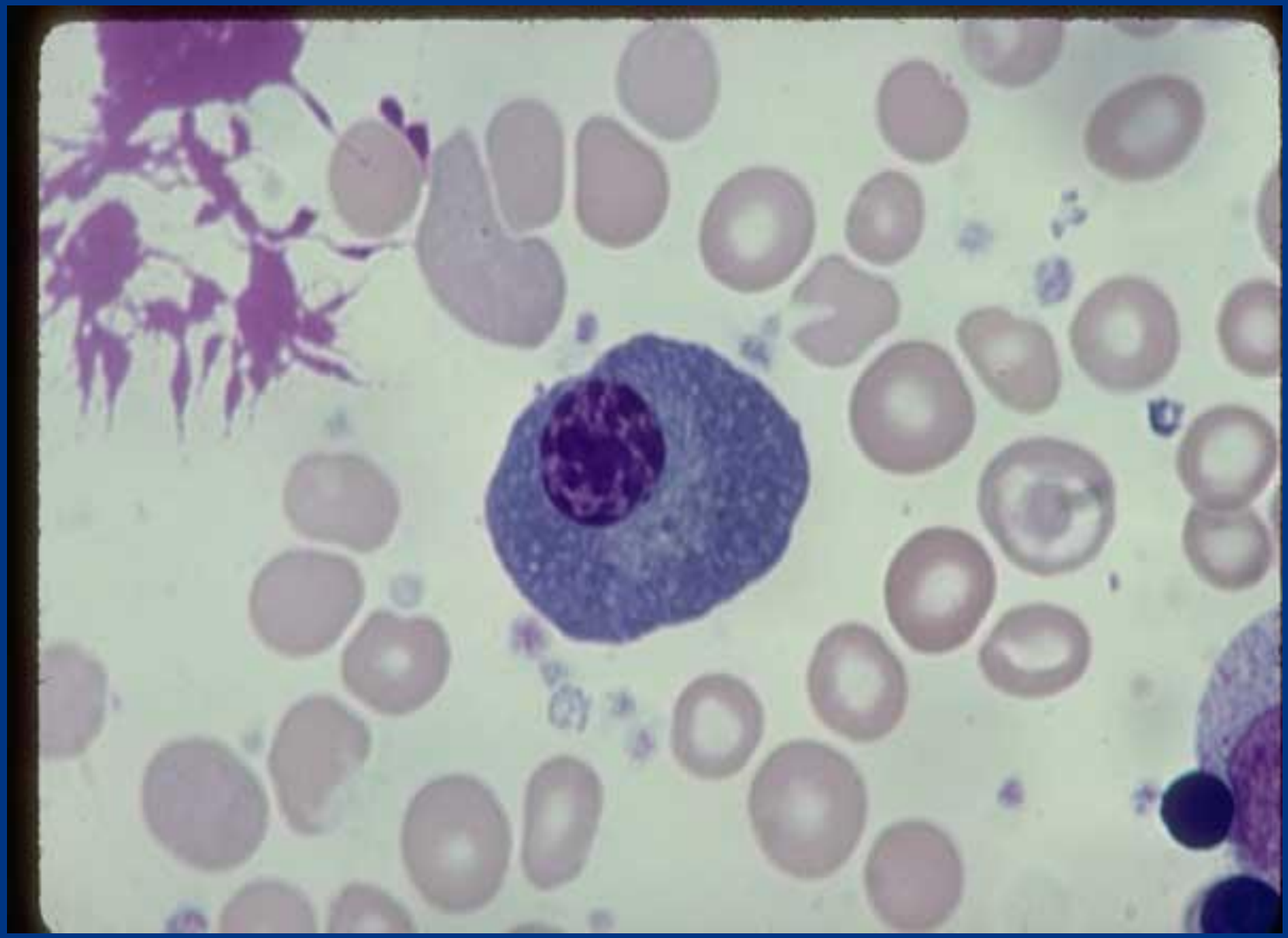
Chronic Antibody Mediated Rejection

- Bad prognosis—4 yr graft survival ~40%
- Cause: Antibody “associated” but may also become independent of DSA
- No effective treatment

What to do?

- Velacade x 8 doses (2 cycles)
- Plasma exchange daily x 5
- High dose IVIG

Nothing really works



American Journal of Transplantation 2009; 9: 201–209
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2008.02461.x

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The Impact of Proteasome Inhibition on Alloantibody-Producing Plasma Cells In Vivo

Tayyab S. Diwan,[1] Suresh Raghavaiah,[1] Justin M. Burns,[1] Walter K. Kremers,[2] James M. Gloor,[3] and Mark D. Stegall[1,4]

Down-Regulating Humoral Immune Responses: Implications for Organ Transplantation

Mark D. Stegall,[1,3] Natalie Moore,[1] Timucin Taner,[2] Han Li,[2] and Patrick G. Dean[2]

Alloantibody can be a major barrier to successful organ transplantation; however, therapy to control antibody production or to alter its impact on the allograft remains limited. The goal of this review is to examine the regulatory steps that are involved in the generation of alloreactive B cells, with a specific emphasis on how known mechanisms relate to clinical situations in transplant recipients. Thus, we will examine the process of activation of mature, naïve B

of long-lived plasma cells in persistent antibody

ed. The regulation of memory B cells and their

review current therapeutic approaches aimed at

controlling alloantibody and assess their efficacy. By examining the pathways to antibody production mechanistically,

Transplantation 2013

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May not be treatable

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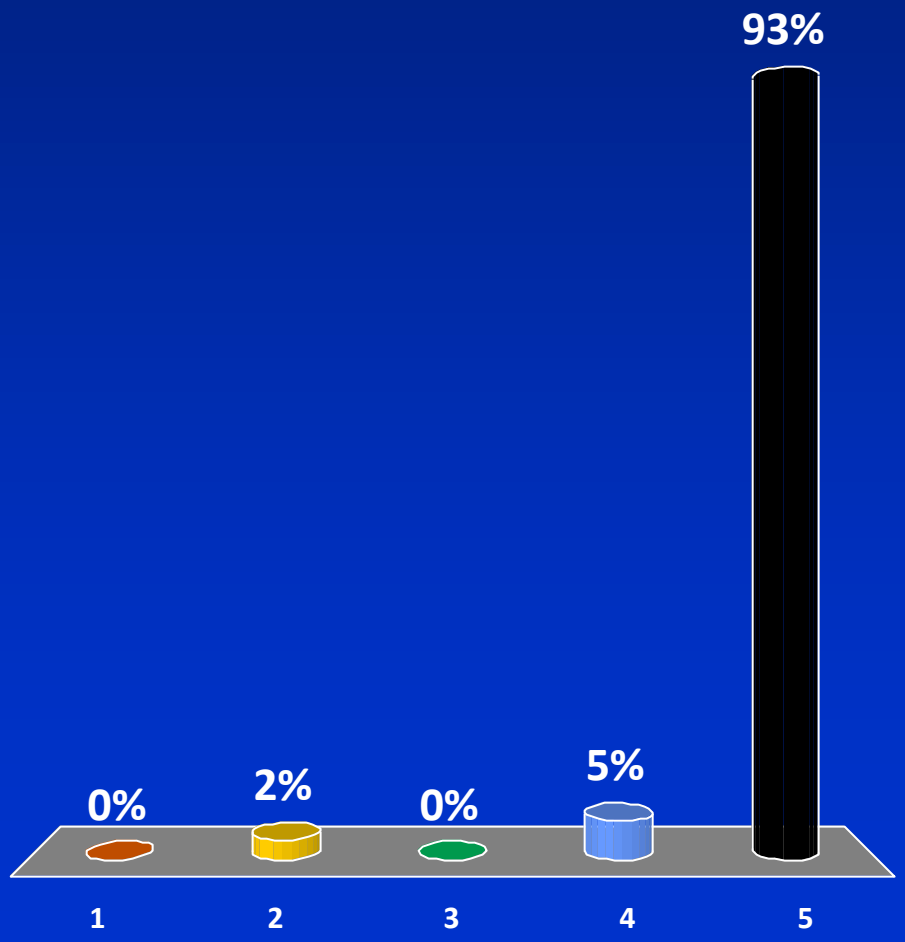
Acute antibody mediated rejection in the first 2 weeks after transplant is:

1. Common in sensitized patients
2. Associated with high levels of donor specific alloantibody
3. C4d+
4. Treated with either/or Plasma exchange and eculizumab
5. All of the above



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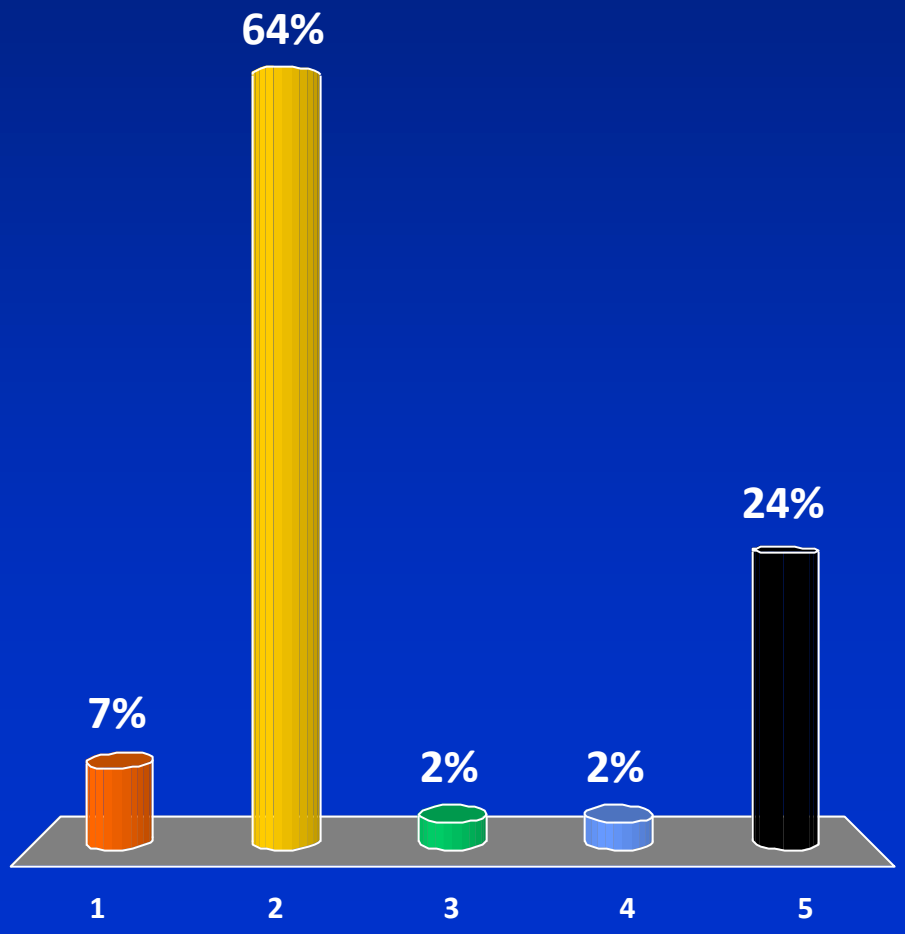
Acute antibody mediated rejection 1 year after transplantation is:

1. More common in sensitized patients
2. Commonly mixed with cellular rejection
3. Treated with velcade
4. Always requires plasma exchange
5. All of the above



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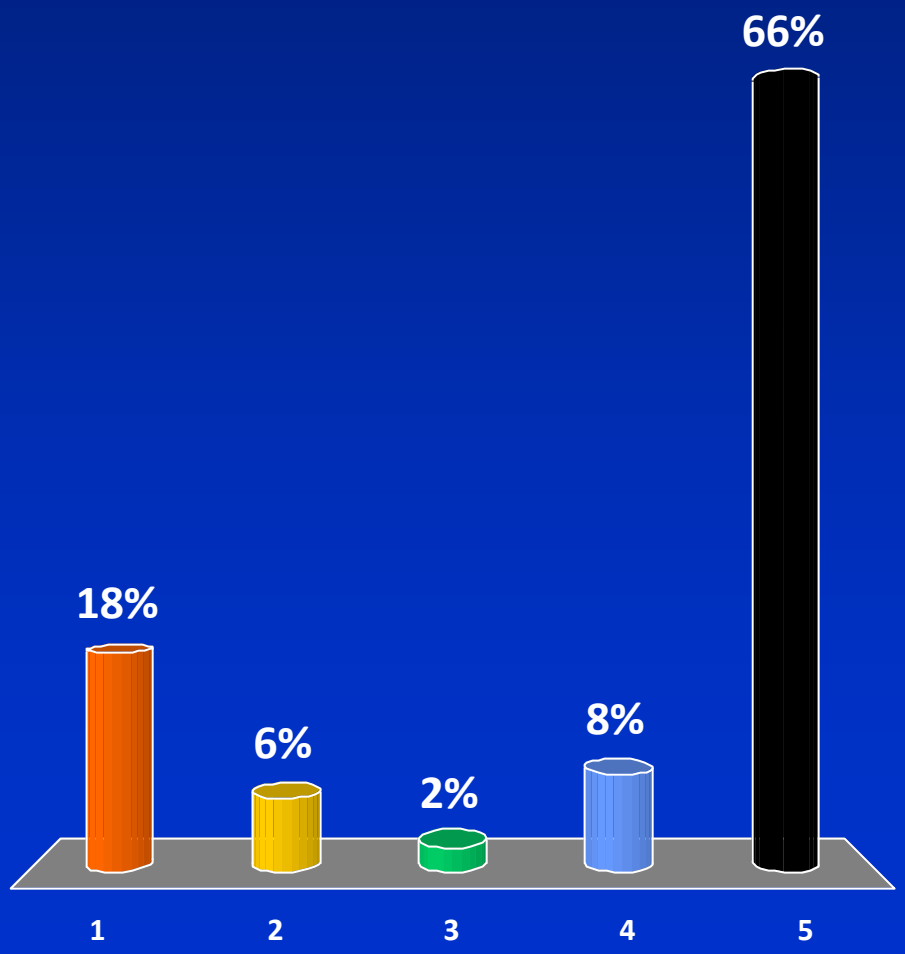
Chronic antibody mediated rejection 3 years after transplantation is:

1. Commonly mixed with cellular rejection
2. Commonly associated with high levels of DSA
3. Always C4d+
4. Requires plasma exchange therapy
5. None of the above



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