Brigham and Women's Hospital
Founding Member, Mass General Brigham

EARLY POST-TRANSPLANT MANAGEMENT

Anil Chandraker MD FRCP FASN FAST
Chief of Renal Medicine
UMass Chan Medical School
Lecturer (Part-Time)
Harvard Medical School

CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Anil Chandraker MD

- Glasgow University Medical School
- Medicine Residency, Manchester Royal Infirmary
- Nephrology Fellowship@West Midlands
- Nephrology Fellowship @BWH/MGH
- Professor of Medicine@UMass Chan Med School
  - Clinical focus: Kidney Transplantation
  - Research focus: Regulatory T cells, BK Nephropathy, Tx Genetics

Disclosures

- Vertex: Chair, Drug Monitoring Committee, VX20-880 and VX20- 264 studies
- Amgen: Investigator Initiated Rapatha Rx in Transplant patients
- Natera: Renasight Scientific Advisory Board
- BioHope: Scientific Advisory Board
- Sanofi: Scientific Advisory Board
- Alexion: Scientific Advisory Board
- NIH: DSMB THINKER Study

Objectives

- Case Based Approach to:

  Discuss differential diagnosis and management of early post transplant graft dysfunction.

CHOOSING INDUCTION THERAPY

Patient 1

40-year-old Caucasian male patient with ESRD due to PKD.
History of HD for 5 years.

- Deceased donor kidney (A2B0DR1 mismatch)
- cPRA Class I is 0 % and Class II is 0 %
- T cell crossmatch negative

	Recipient	Donor
ABO	O	O
CMV	+	-
EBV	-	+

No history of malignancy
You plan to initiate induction therapy.

Which one of the following statements is correct regarding current use of induction therapy in the USA?

A: No induction therapy - his PRA is 0% and his CXM is negative

B: No induction therapy should be used as he is a younger patient and less likely to have a memory T cell response against the allograft

C: Use of induction therapy reduces the risk of acute rejection but does not improve allograft survival

D: Thymoglobulin will be the most commonly used agent in this case

E: He should receive Basiliximab as it is more likely to target a $CD25^{+}$ regulatory T cell response

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A: No induction therapy - his PRA is 0% and his cytotoxic CXM is negative

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Why use induction therapy?

- Reduce rates of acute rejection

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- Reduce rates of acute rejection
- Avoid delayed graft function

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- Reduce rates of acute rejection
- Avoid delayed graft function
- Minimize maintenance immunosuppression

Why use induction therapy?

- Reduce rates of acute rejection

  - Acute rejection was strongly correlated with long term allograft outcomes

Why have acute rejection rates fallen?

- Induction therapy
- Better HLA matching
- Stronger maintenance immunosuppression

Choice of Induction Agent

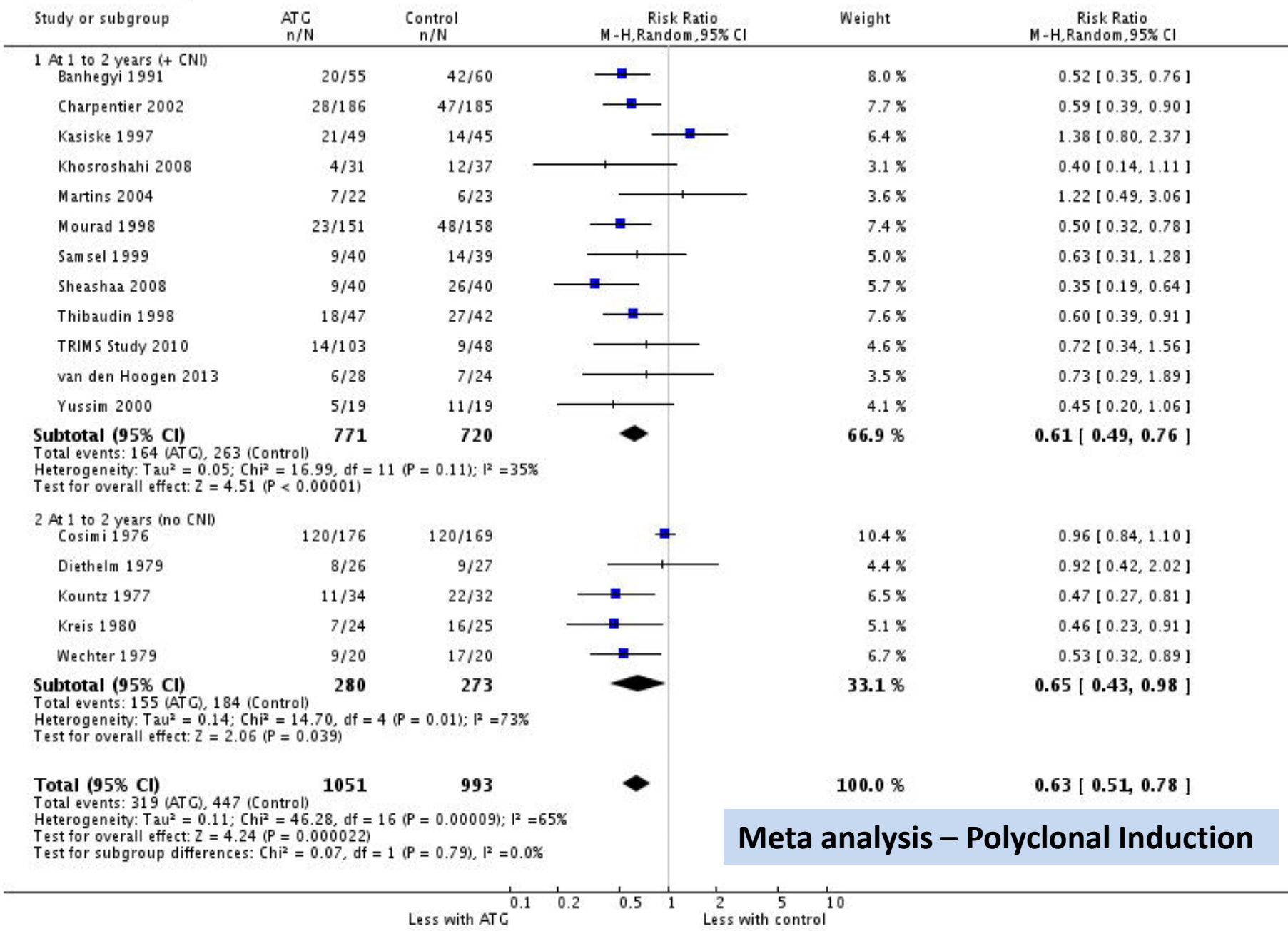
- Depleting (High immunological risk)
  - Anti Thymocyte Globulin (ATG) - 3-6 mg/kg in divided doses
  - Alemtuzumab (anti CD52)
    - Results in transient non-specific lymphopenia

- Non-Depleting (Low immunological risk)
  - Anti IL-2r (Basiliximab) 20 mg IV on day 0 & 4
    - Targets IL-2 receptor on T cells – IL-2 is a key autocrine required for T cell survival

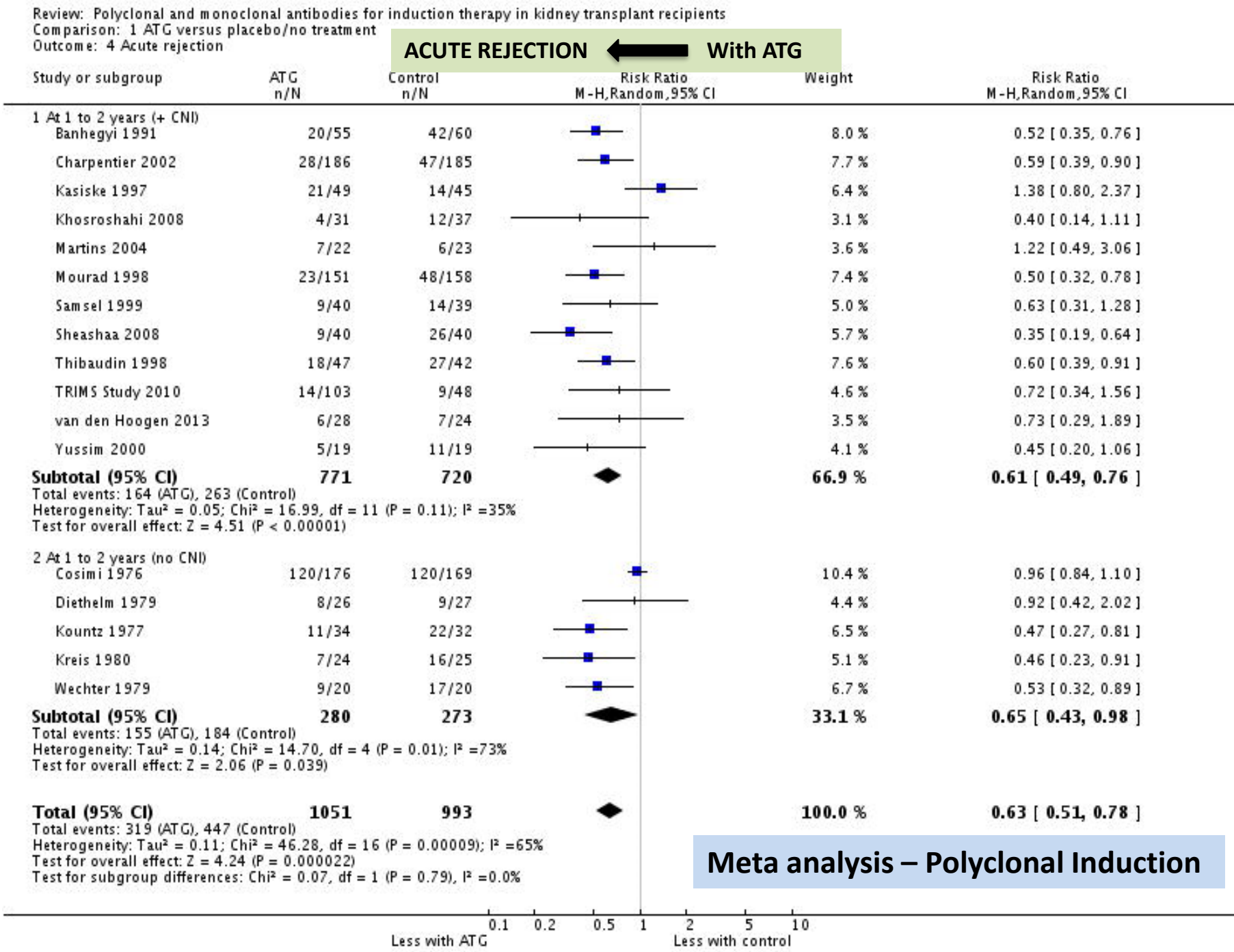
- Belatacept (Not really an induction therapy)
  - CTLA4Ig – binds B7 (CD80/86) prevents signal 2 and thus T cell activation – Cannot be given in EBV negative recipients

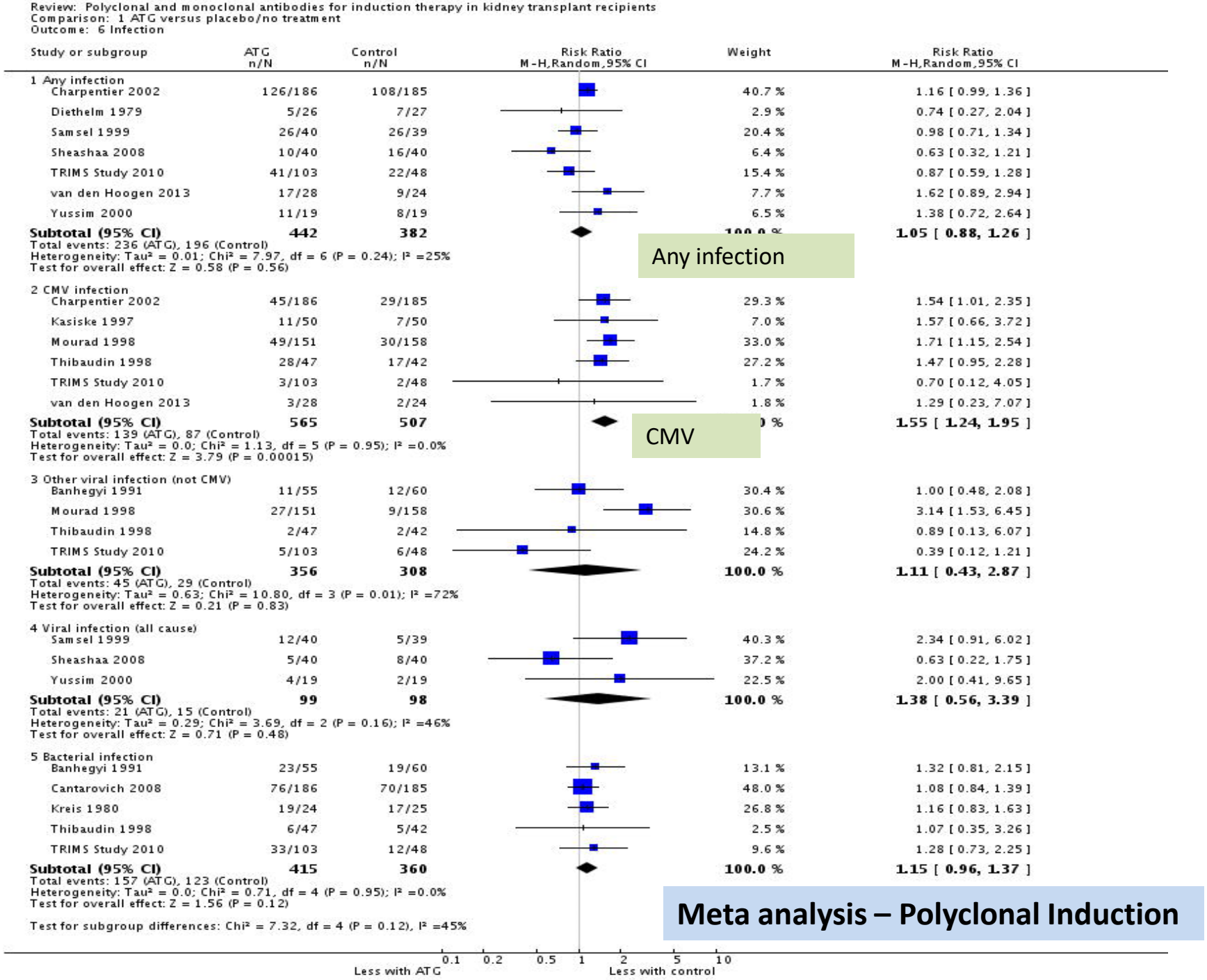
Review: Polyclonal and monoclonal antibodies for induction therapy in kidney transplant recipients
Comparison: 1 ATG versus placebo/no treatment
Outcome: 4 Acute rejection

With ATG

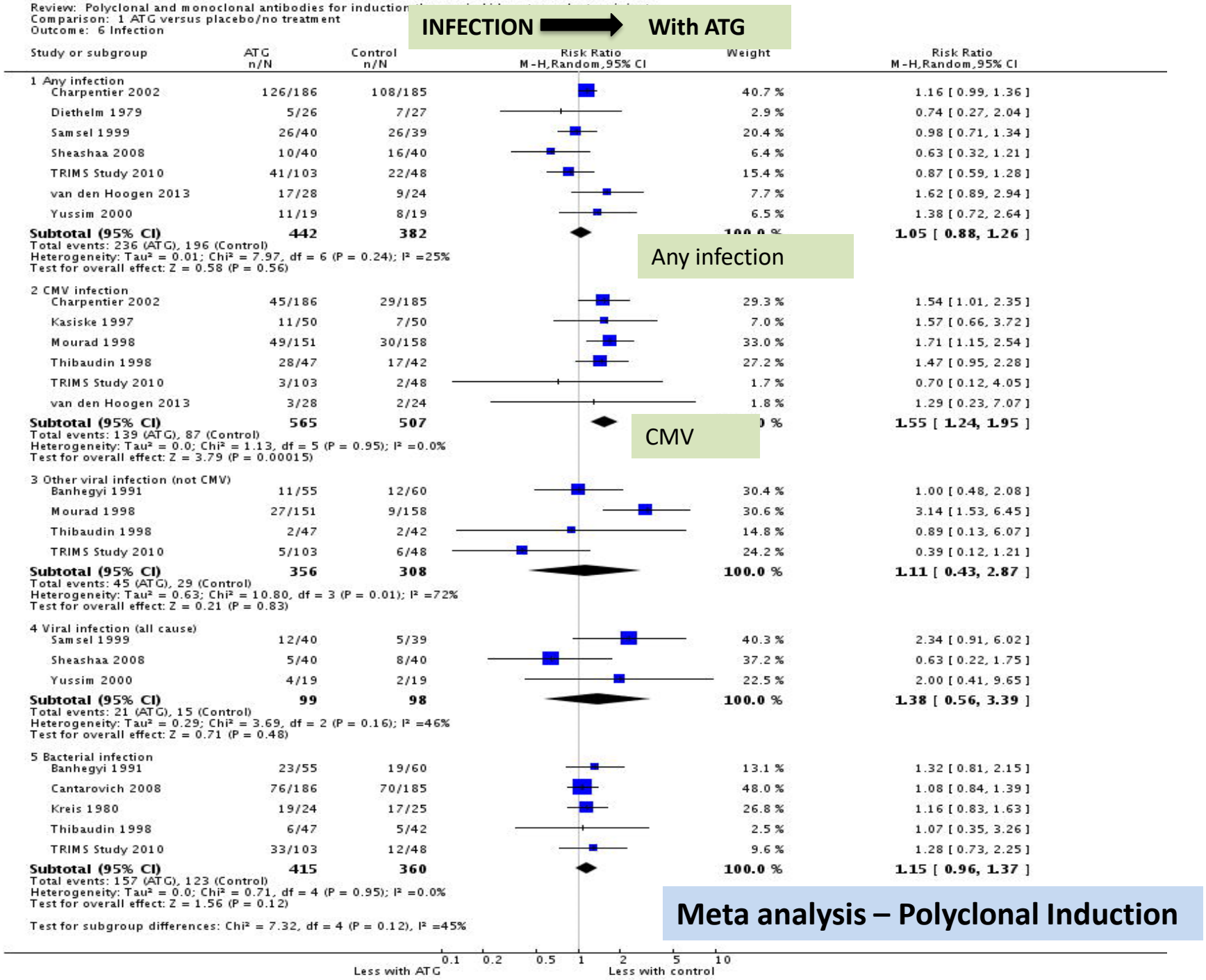


Meta analysis – Polyclonal Induction


Review: Polyclonal and monoclonal antibodies for induction therapy in kidney transplant recipients
Comparison: 1 ATG versus placebo/no treatment
Outcome: 4 Acute rejection
ACUTE REJECTION
With ATG
Study or subgroup
ATG n/N
Control n/N
Risk Ratio M-H,Random,95% CI
Weight
Risk Ratio M-H,Random,95% CI
1 At 1 to 2 years (+ CNI)
Banhegyi 1991 20/55 42/60 8.0 % 0.52 [0.35, 0.76]
Charpentier 2002 28/186 47/185 7.7 % 0.59 [0.39, 0.90]
Kasiske 1997 21/49 14/45 6.4 % 1.38 [0.80, 2.37]
Khosroshahi 2008 4/31 12/37 3.1 % 0.40 [0.14, 1.11]
Martins 2004 7/22 6/23 3.6 % 1.22 [0.49, 3.06]
Mourad 1998 23/151 48/158 7.4 % 0.50 [0.32, 0.78]
Samsel 1999 9/40 14/39 5.0 % 0.63 [0.31, 1.28]
Sheashaa 2008 9/40 26/40 5.7 % 0.35 [0.19, 0.64]
Thibaudin 1998 18/47 27/42 7.6 % 0.60 [0.39, 0.91]
TRIMS Study 2010 14/103 9/48 4.6 % 0.72 [0.34, 1.56]
van den Hoogen 2013 6/28 7/24 3.5 % 0.73 [0.29, 1.89]
Yussim 2000 5/19 11/19 4.1 % 0.45 [0.20, 1.06]
Subtotal (95% CI) 771 720 66.9 % 0.61 [0.49, 0.76]
Total events: 164 (ATG), 263 (Control)
Heterogeneity: Tau² = 0.05; Chi² = 16.99, df = 11 (P = 0.11); I² =35%
Test for overall effect: Z = 4.51 (P < 0.00001)
2 At 1 to 2 years (no CNI)
Cosimi 1976 120/176 120/169 10.4 % 0.96 [0.84, 1.10]
Diethelm 1979 8/26 9/27 4.4 % 0.92 [0.42, 2.02]
Kountz 1977 11/34 22/32 6.5 % 0.47 [0.27, 0.81]
Kreis 1980 7/24 16/25 5.1 % 0.46 [0.23, 0.91]
Wechter 1979 9/20 17/20 6.7 % 0.53 [0.32, 0.89]
Subtotal (95% CI) 280 273 33.1 % 0.65 [0.43, 0.98]
Total events: 155 (ATG), 184 (Control)
Heterogeneity: Tau² = 0.14; Chi² = 14.70, df = 4 (P = 0.01); I² =73%
Test for overall effect: Z = 2.06 (P = 0.039)
Total (95% CI) 1051 993 100.0 % 0.63 [0.51, 0.78]
Total events: 319 (ATG), 447 (Control)
Heterogeneity: Tau² = 0.11; Chi² = 46.28, df = 16 (P = 0.00009); I² =65%
Test for overall effect: Z = 4.24 (P = 0.000022)
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² =0.0%
0.1 0.2 0.5 1 2 5 10
Less with ATG
Less with control
Meta analysis – Polyclonal Induction



Meta analysis – Polyclonal Induction


Review: Polyclonal and monoclonal antibodies for induction
Comparison: 1 ATG versus placebo/no treatment
Outcome: 6 Infection
INFECTION With ATG
Study or subgroup
ATG n/N
Control n/N
Risk Ratio M-H,Random,95% CI
Weight
Risk Ratio M-H,Random,95% CI
1 Any infection
Charpentier 2002 126/186 108/185 40.7 % 1.16 [0.99, 1.36]
Diethelm 1979 5/26 7/27 2.9 % 0.74 [0.27, 2.04]
Samsel 1999 26/40 26/39 20.4 % 0.98 [0.71, 1.34]
Sheashaa 2008 10/40 16/40 6.4 % 0.63 [0.32, 1.21]
TRIMS Study 2010 41/103 22/48 15.4 % 0.87 [0.59, 1.28]
van den Hoogen 2013 17/28 9/24 7.7 % 1.62 [0.89, 2.94]
Yussim 2000 11/19 8/19 6.5 % 1.38 [0.72, 2.64]
Subtotal (95% CI) 442 382 1.05 [0.88, 1.26]
Total events: 236 (ATG), 196 (Control)
Heterogeneity: Tau² = 0.01; Chi² = 7.97, df = 6 (P = 0.24); I² =25%
Test for overall effect: Z = 0.58 (P = 0.56)
Any infection
2 CMV infection
Charpentier 2002 45/186 29/185 29.3 % 1.54 [1.01, 2.35]
Kasiske 1997 11/50 7/50 7.0 % 1.57 [0.66, 3.72]
Mourad 1998 49/151 30/158 33.0 % 1.71 [1.15, 2.54]
Thibaudin 1998 28/47 17/42 27.2 % 1.47 [0.95, 2.28]
TRIMS Study 2010 3/103 2/48 1.7 % 0.70 [0.12, 4.05]
van den Hoogen 2013 3/28 2/24 1.8 % 1.29 [0.23, 7.07]
Subtotal (95% CI) 565 507 1.55 [1.24, 1.95]
Total events: 139 (ATG), 87 (Control)
Heterogeneity: Tau² = 0.0; Chi² = 1.13, df = 5 (P = 0.95); I² =0.0%
Test for overall effect: Z = 3.79 (P = 0.00015)
CMV
3 Other viral infection (not CMV)
Banhegyi 1991 11/55 12/60 30.4 % 1.00 [0.48, 2.08]
Mourad 1998 27/151 9/158 30.6 % 3.14 [1.53, 6.45]
Thibaudin 1998 2/47 2/42 14.8 % 0.89 [0.13, 6.07]
TRIMS Study 2010 5/103 6/48 24.2 % 0.39 [0.12, 1.21]
Subtotal (95% CI) 356 308 100.0 % 1.11 [0.43, 2.87]
Total events: 45 (ATG), 29 (Control)
Heterogeneity: Tau² = 0.63; Chi² = 10.80, df = 3 (P = 0.01); I² =72%
Test for overall effect: Z = 0.21 (P = 0.83)
4 Viral infection (all cause)
Samsel 1999 12/40 5/39 40.3 % 2.34 [0.91, 6.02]
Sheashaa 2008 5/40 8/40 37.2 % 0.63 [0.22, 1.75]
Yussim 2000 4/19 2/19 22.5 % 2.00 [0.41, 9.65]
Subtotal (95% CI) 99 98 100.0 % 1.38 [0.56, 3.39]
Total events: 21 (ATG), 15 (Control)
Heterogeneity: Tau² = 0.29; Chi² = 3.69, df = 2 (P = 0.16); I² =46%
Test for overall effect: Z = 0.71 (P = 0.48)
5 Bacterial infection
Banhegyi 1991 23/55 19/60 13.1 % 1.32 [0.81, 2.15]
Cantarovich 2008 76/186 70/185 48.0 % 1.08 [0.84, 1.39]
Kreis 1980 19/24 17/25 26.8 % 1.16 [0.83, 1.63]
Thibaudin 1998 6/47 5/42 2.5 % 1.07 [0.35, 3.26]
TRIMS Study 2010 33/103 12/48 9.6 % 1.28 [0.73, 2.25]
Subtotal (95% CI) 415 360 100.0 % 1.15 [0.96, 1.37]
Total events: 157 (ATG), 123 (Control)
Heterogeneity: Tau² = 0.0; Chi² = 0.71, df = 4 (P = 0.95); I² =0.0%
Test for overall effect: Z = 1.56 (P = 0.12)
Test for subgroup differences: Chi² = 7.32, df = 4 (P = 0.12), I² =45%
0.1 0.2 0.5 1 2 5 10
Less with ATG
Less with control
Meta analysis – Polyclonal Induction

KDIGO guidelines

Patients with one or more of the following risk factor are considered high risk for acute rejection and should have depletional induction therapy:

- Presence of a donor-specific antibody (DSA)
- Panel reactive antibody (PRA) greater than 0 percent
- Blood group incompatibility
- Cold ischemia time greater than 24 hours/Delayed onset of graft function
- African-American ethnicity (in the United States)

- Increased number of HLA mismatches
- Younger recipient and older donor age

Patient 1

40-year-old Caucasian male patient with ESRD due to PKD.
History of HD for 5 years.

- Deceased donor kidney (A2B0DR1 mismatch)
- cPRA Class I is 0 % and Class II is 0 %
- T cell crossmatch negative

	Recipient	Donor
ABO	O	O
CMV	+	-
EBV	-	+

No history of malignancy
You plan to initiate induction therapy.

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	Recipient	Donor
ABO	O	O
CMV	+	-
EBV	-	+

No history of malignancy
You plan to initiate induction therapy

History of ITP with platelet count of 70,000 per cubic millimeter

Now what is your first choice for induction therapy?

A- Thymoglobulin

B- Basiliximab

C- Alemtuzumab

D- Belatacept

D- No induction therapy

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A- Thymoglobulin

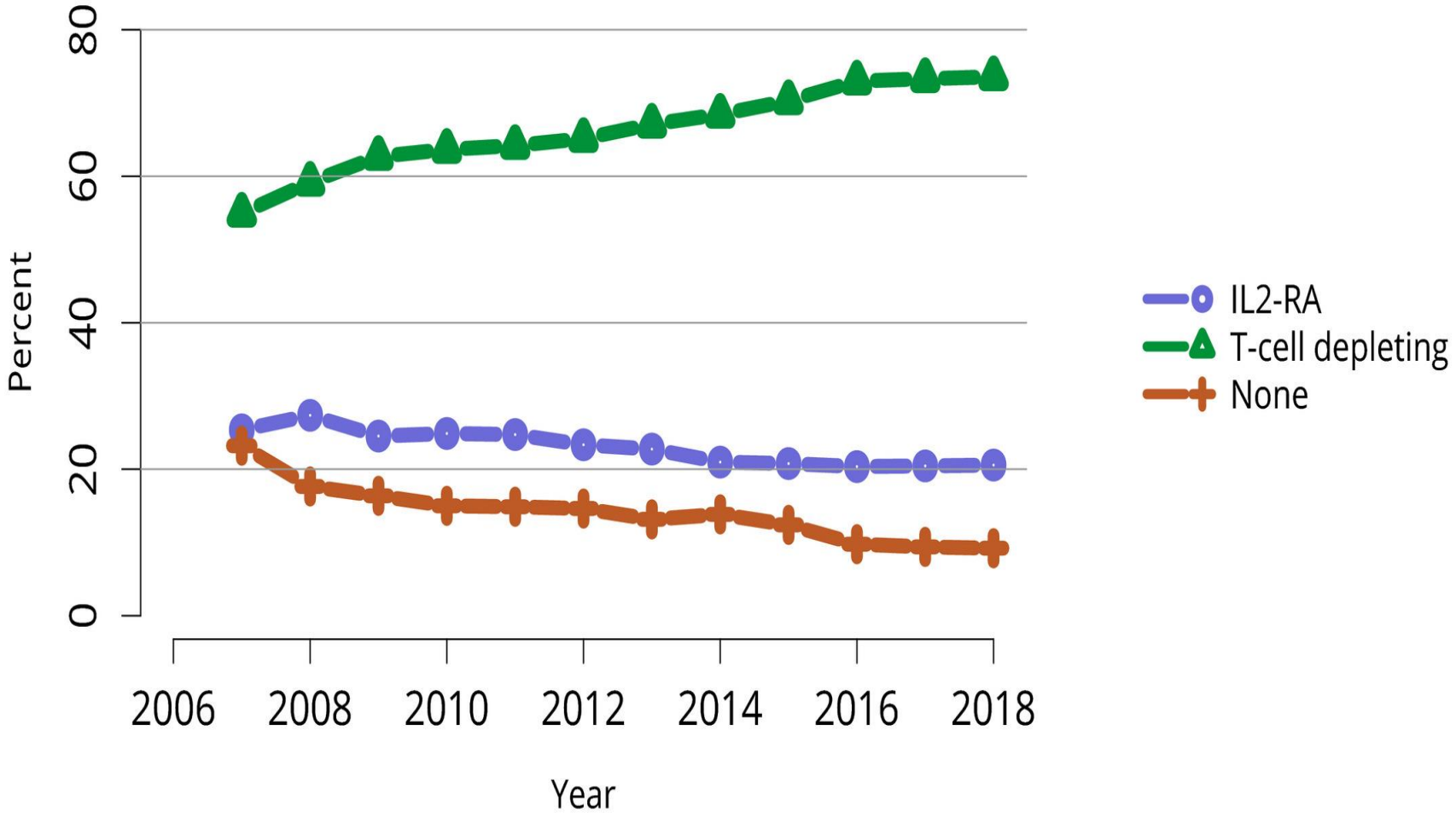
B- Basiliximab

C- Alemtuzumab

D- Belatacept

D- No induction therapy

OPTN/SRTR 2018 Annual Data Report: Kidney



American J Transplantation, Volume: 20, Issue: s1, Pages: 20-130, First published: 02 January 2020, DOI: (10.1111/ajt.15672)

CHOOSING MAINTENANCE IMMUNOTHERAPY

Patient 1

40-year-old Caucasian male patient with ESRD due to PKD.
History of HD for 5 years.

- Deceased donor kidney (A2B0DR1 mismatch)
- cPRA Class I is 0 % and Class II is 0 %
- CDC AHG-T cell crossmatch negative

	Recipient	Donor
ABO	O	O
CMV	+	-
EBV	-	+

No history of malignancy
You plan to initiate induction therapy

History of ITP with platelet count of 70,000 per cubic millimeter

Received Basiliximab induction treatment

Which one of the following statements is correct?

A: The most commonly used regimen will be triple therapy using tacrolimus, mycophenolate and prednisone.

B: Tacrolimus can be held if delayed graft function is present

C: There is a 50% chance the patient is a ‘rapid metabolizer’ of tacrolimus and should be dosed appropriately

D: Prednisone withdrawal is an absolute contraindication

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A: The most commonly used regimen will be triple therapy using tacrolimus, mycophenolate and prednisone.

B: Tacrolimus can be held if delayed graft function is present

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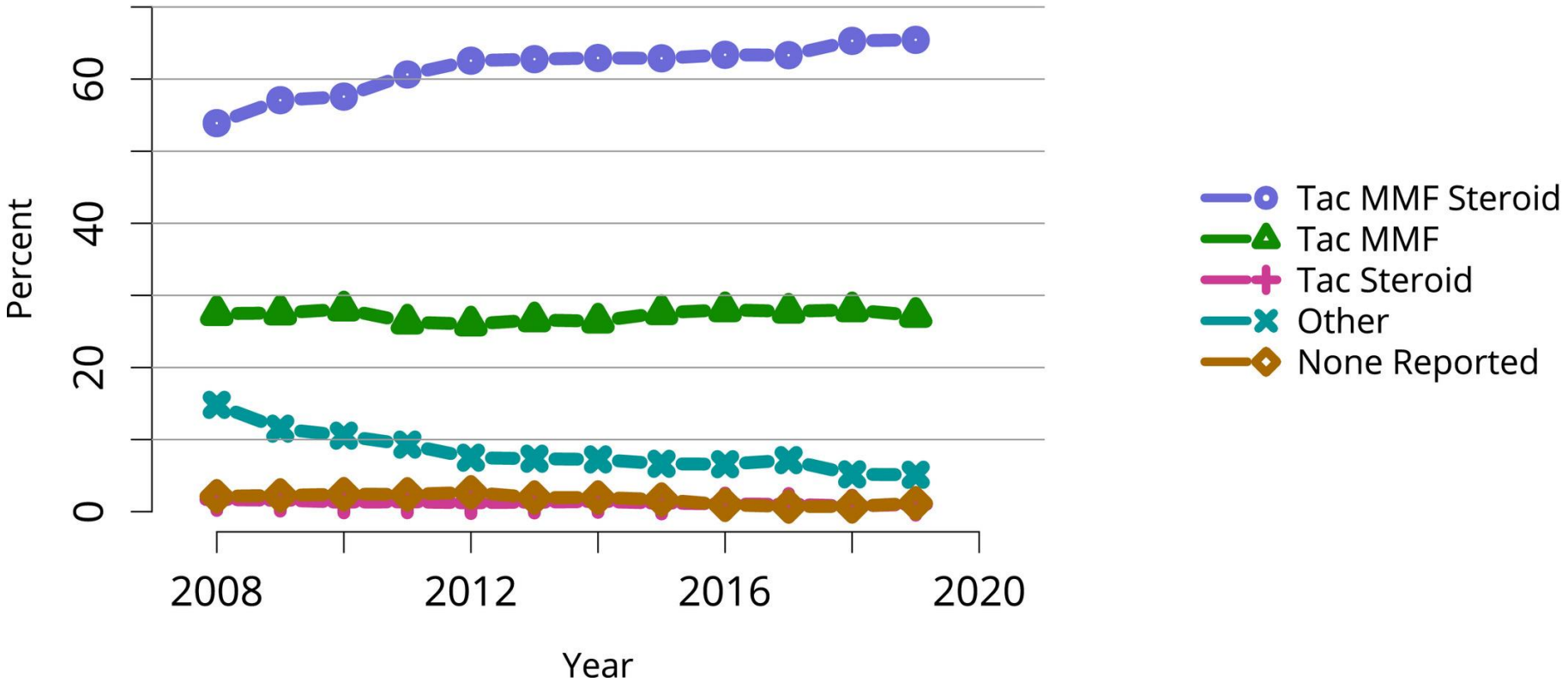
D: Prednisone withdrawal is an absolute contraindication

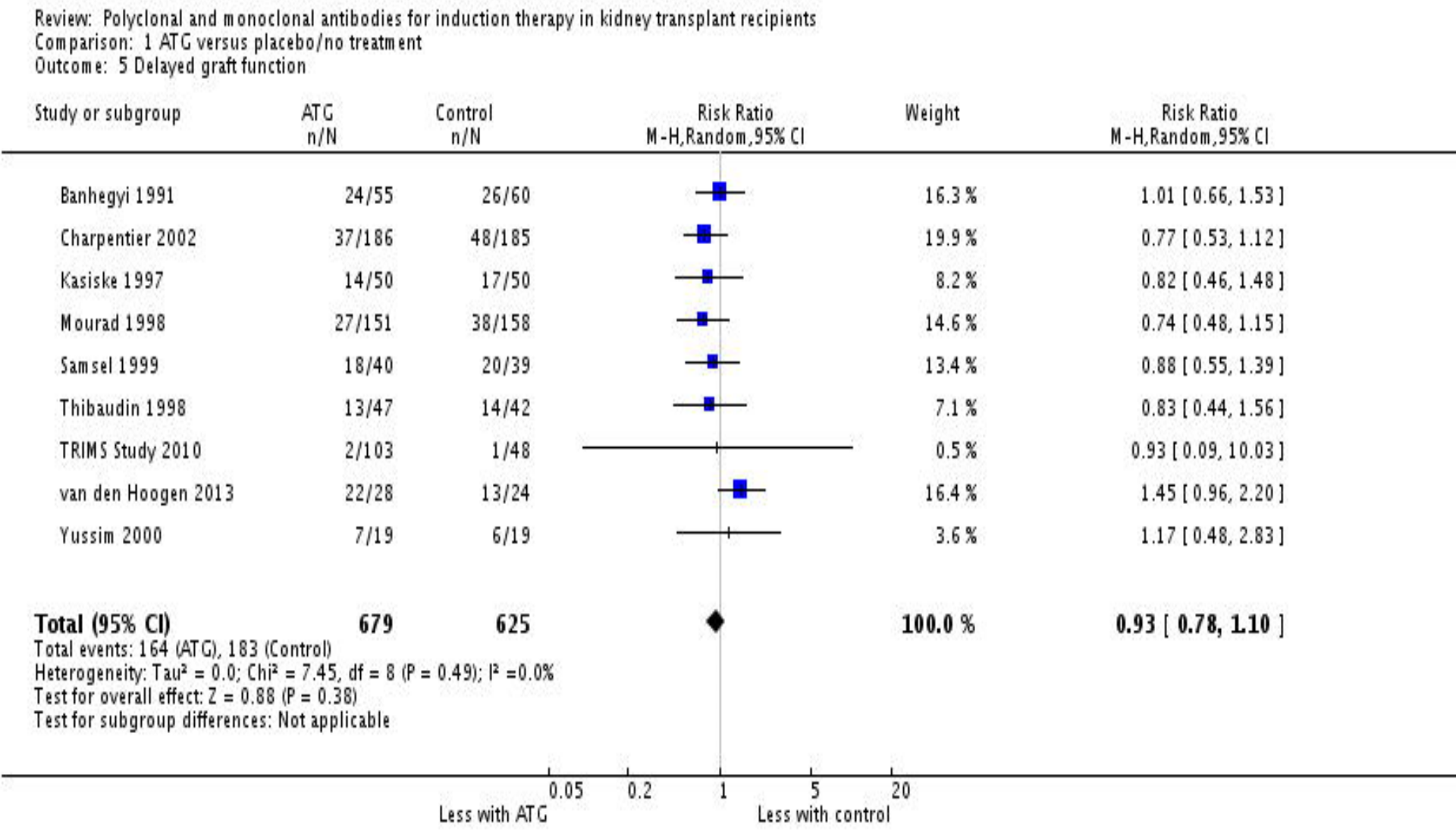
Immunosuppression regimen use in adult kidney transplant recipients.



OPTN/SRTR 2019 Annual Data Report: Kidney

American Journal of Transplantation, Volume: 21, Issue: S2, 17 February 2021, DOI:(10.1111/ajt.16502)

Delayed Graft Function Less with ATG



DELAYED AND SLOW GRAFT FUNCTION

Patient 2

58 year old African American female with ESRD due to presumed hypertension.

PD for 10 years.

- Deceased donor kidney (A2B2DR2 mismatch)
- cPRA Class I is 0 % and Class II is 0 %.
- T cell crossmatch negative .

	Recipient	Donor
ABO	O	O
CMV	+	+
EBV	+	+

Patient was induced with ATG and started on steroid and mycophenolate

The surgery was uneventful

Post-op Day 1, urine output is 5-10cc/hour, Cr 7.5 –> 8.5 mg/dl & K 6.5.

Delayed graft function (DGF)

- Defined as need for dialysis in the first post-transplant week
  - It is an acute kidney injury in transplanted kidney and should be worked up accordingly (Pre-renal, renal, Post-renal)
- Slowed graft function: creatinine is coming down slowly (impaired early graft function)
  - Also defined as Cr > 3 mg/dl by POD 5 but no dialysis required.
- Primary non-function: <5%

Humar A. et al. Clin Transplant. 1997. Dec 11(6): 623-7.

Etiology of DGF

Pre-renal:

- Hypotension: anesthesia, induction therapy
- Volume depletion
- Donor Disease *eg* microthrombi

Renal:

- Post-ischemic acute tubular necrosis:
  - Recipient and donor risk factors
- Acute CNI toxicity
- Hyper-acute rejection (HAR)
- Acute Antibody mediated rejection (AMR)
- Recurrent Disease

Post Renal:

- Obstruction can be painless

Important information in formulating a differential diagnosis of DGF

- Donor factors:
  - Age >60
  - HTN
  - ARF
  - Brain death
  - Cardiac arrest
  - Nephrotoxic meds
  - ECD kidneys or KDPI > 85%
  - Obesity
- Procurement surgery:
  - Intra-op hypotension,
  - Prolonged cold ischemia time
  - Prolonged warm ischemia time
- Intra-op:
  - Hypotension
  - Intra-operative diuresis
  - Antibody induction therapy
- Recipient risk factors:
  - Maintenance hemodialysis
  - Obesity,
  - Diabetes,
  - Age > 55,
  - African-American race,
  - Small-for-size organ
  - Immune sensitizing events
  - High dose CNI

Etiology of DGF: Renal

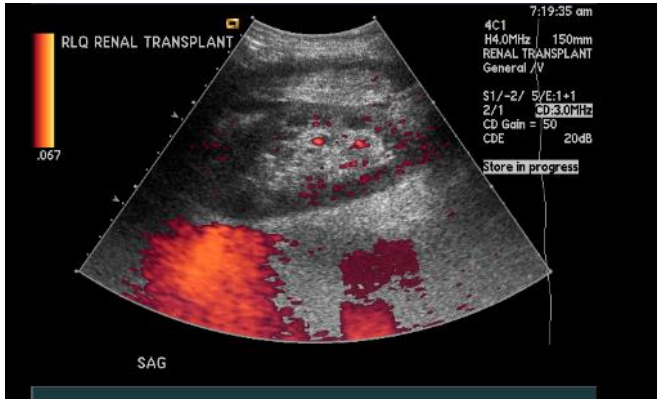
- **Thrombosis**
  - 2-6% of all tx, usually mechanical

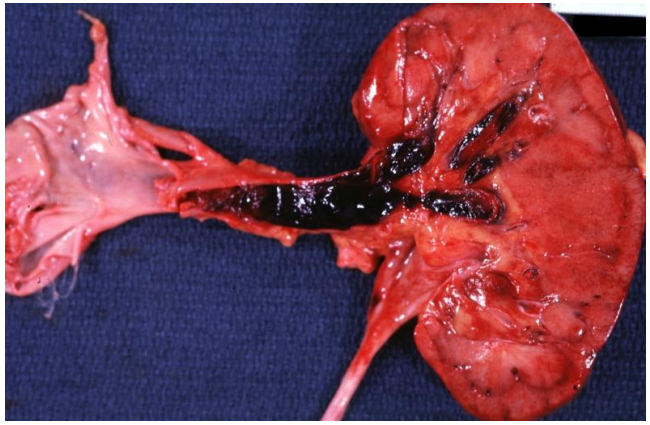
Renal Artery:

  - Hypotension, hyperacute rejection, hypercoagulable state

Renal vein:

  - Can present with sudden pain and swelling
  - Compression, stenosis or hypercoagulable state





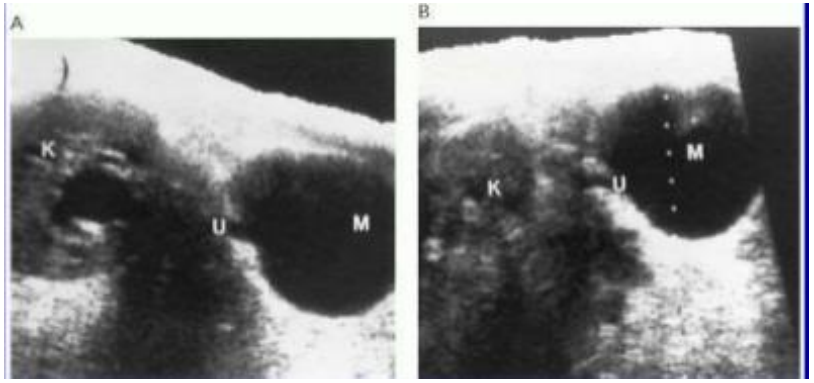
Needs immediate surgical exploration.

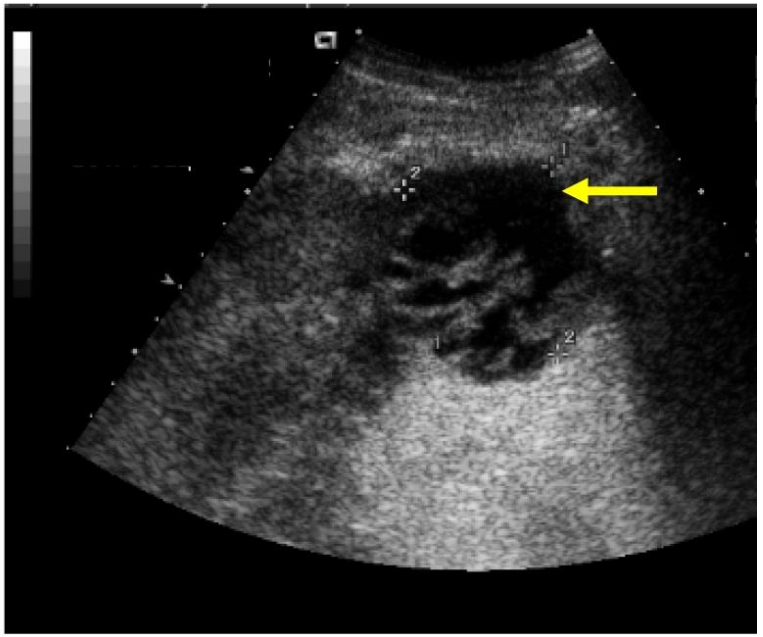
Continued anticoagulation

- **Atheroemboli:** recipient/donor vascular origin

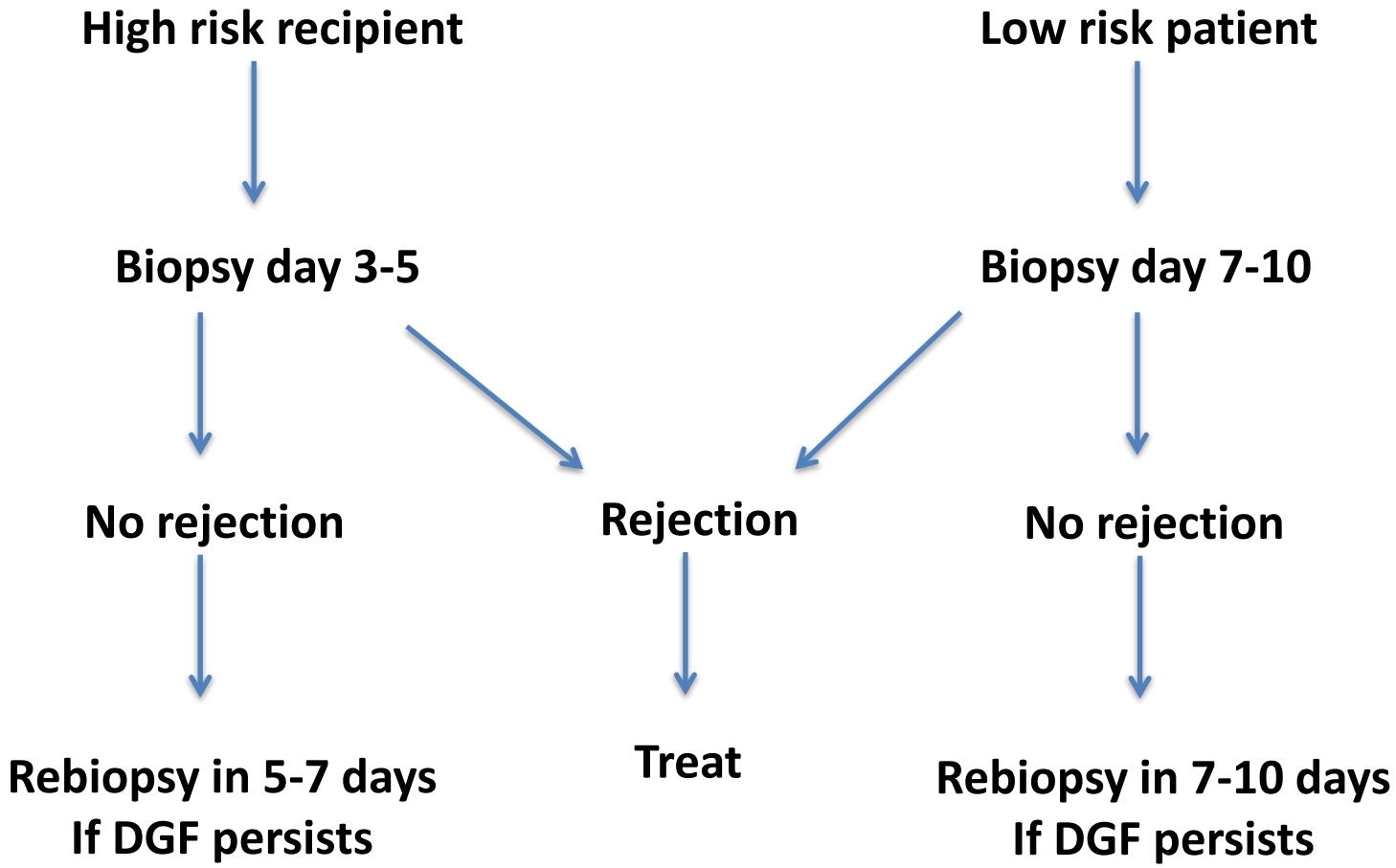
Etiology of DGF: Post renal

- **Ureteral obstruction:**
  - Ureteral necrosis
  - Faulty anastomosis
  - Neurogenic bladder
  - BPH
- **Urine leak/urinoma:**
  - Ureteral infarction
  - UV anastomosis failure
  - Perinephric to hydronephrosis
  - Urine and the JP fluid creatinine





DGF/AR Algorithm



EARLY POST TRANSPLANT KIDNEY DYSFUNCTION (AFTER THE FIRST WEEK)

Patient 2

58 year old African American female with ESRD due to presumed hypertension. PD for 10 years,

Deceased donor kidney (A2B2DR2 mismatch)
cPRA Class I is 0 % and Class II is 0 %.
CDC AHG-T cell crossmatch negative .

Patient was induced with ATG and started on steroid and mycophenolate
The surgery was uneventful. Tacrolimus is started on day 2
Post-op Day 1, urine output is 5-10cc/hour, Cr 7.5 –> 8.5 mg/dl & K 6.5

Post-op Day 7 - Improving , urine output 2.5L/24 hours, creatinine 1.8

Post-op Day 10 – Clinic visit

Worsening pain over the incision site

24 hours decrease in urine output

Worsening edema in the right lower extremity

Serum creatinine 2.5 mg/dl

Which one of the following statements is correct?

A: Start IV methylprednisolone and admit for biopsy

B: Most likely diagnosis is RLE DVT extending to renal vein start IV heparin

C: A renal US would likely show a fluid collection with a high level of protein and triglyceride in fluid aspirates compared to serum

D: A renal US would likely show a fluid collection with high level of creatinine in the JP fluid compared to serum

Which one of the following statements is correct?

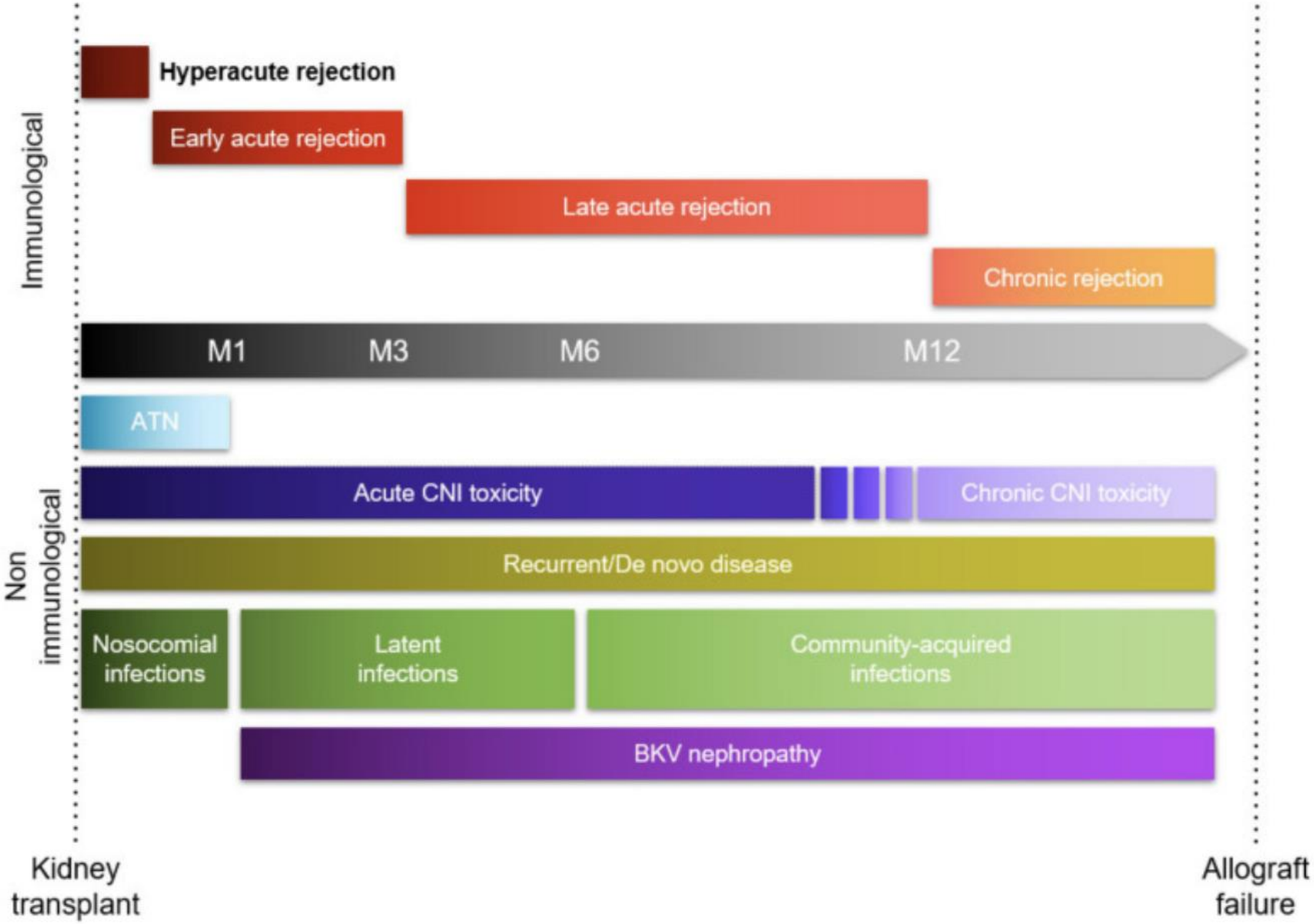
A: Start IV methylprednisolone and admit for biopsy

B: Most likely diagnosis is RLE DVT extending to renal vein start IV heparin

C: A renal US would likely show a fluid collection with a high level of protein and triglyceride in fluid aspirates compared to serum

D: A renal US would likely show a fluid collection with high level of creatinine in the JP fluid compared to serum

Timeline of early and late causes of graft dysfunction.



Quaglia M et al. Recent Advances on Biomarkers of Early and Late Kidney Graft Dysfunction. Int J Mol Sci. 2020 Jul 29;21(15):5404.

Differential Diagnosis

- **Pre-renal**

  Hypotension and volume depletion

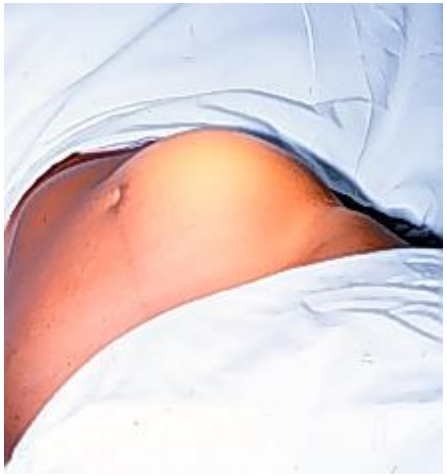
- **“Post-renal”**

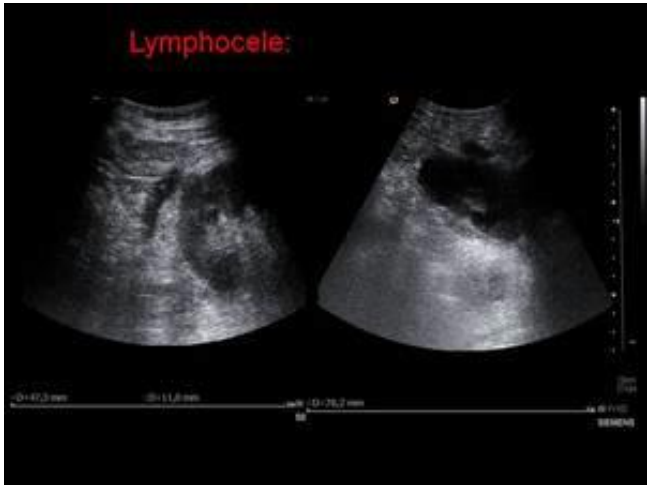
  Neurogenic bladder

  BPH

  Lymphocele:

  - First 3 months post transplant
  - Lymph leaking - severed lymphatics (5-15%).
  - Can cause pain, AKI, urinary frequency, lower extremity edema, iliac vein thrombosis or PE.
  - Diagnosis by U/S.
  - Treatment is percutaneous drainage.





Differential Diagnosis

- **Intrinsic renal**

  Acute rejection: Cellular or Humoral

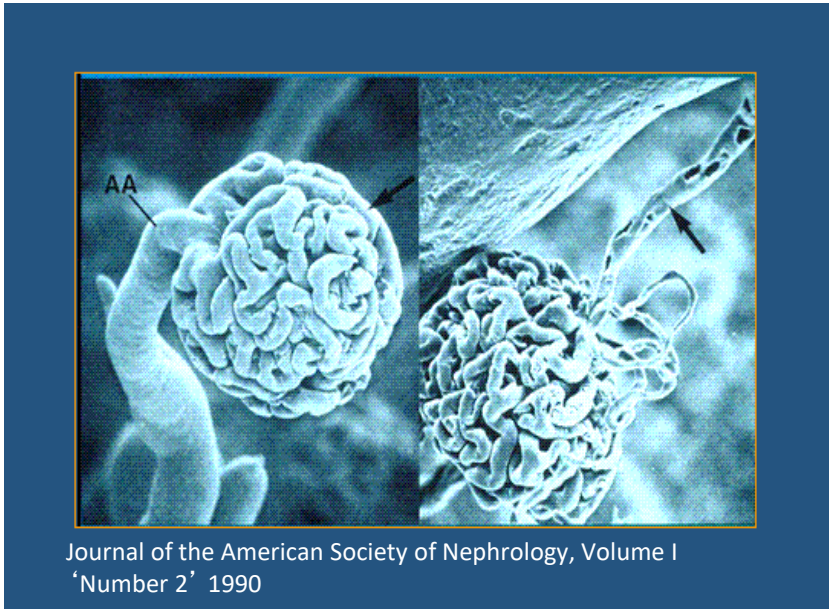
  CNI nephrotoxicity

  Infection:

  – BK nephropathy
  – Cytomegalovirus

  Recurrence of the primary disease:

  – Focal segmental glomerulosclerosis (FSGS),
  – Atypical hemolytic-uremic syndrome (aHUS)
  – Thrombotic thrombocytopenic purpura (TTP)
  – Anti-glomerular basement membrane (GBM) antibody disease



Journal of the American Society of Nephrology, Volume I
'Number 2' 1990

Approach

- Approach: Pre-renal (ATN), Renal (GN,AIN,ACR,AHR), Obstruction

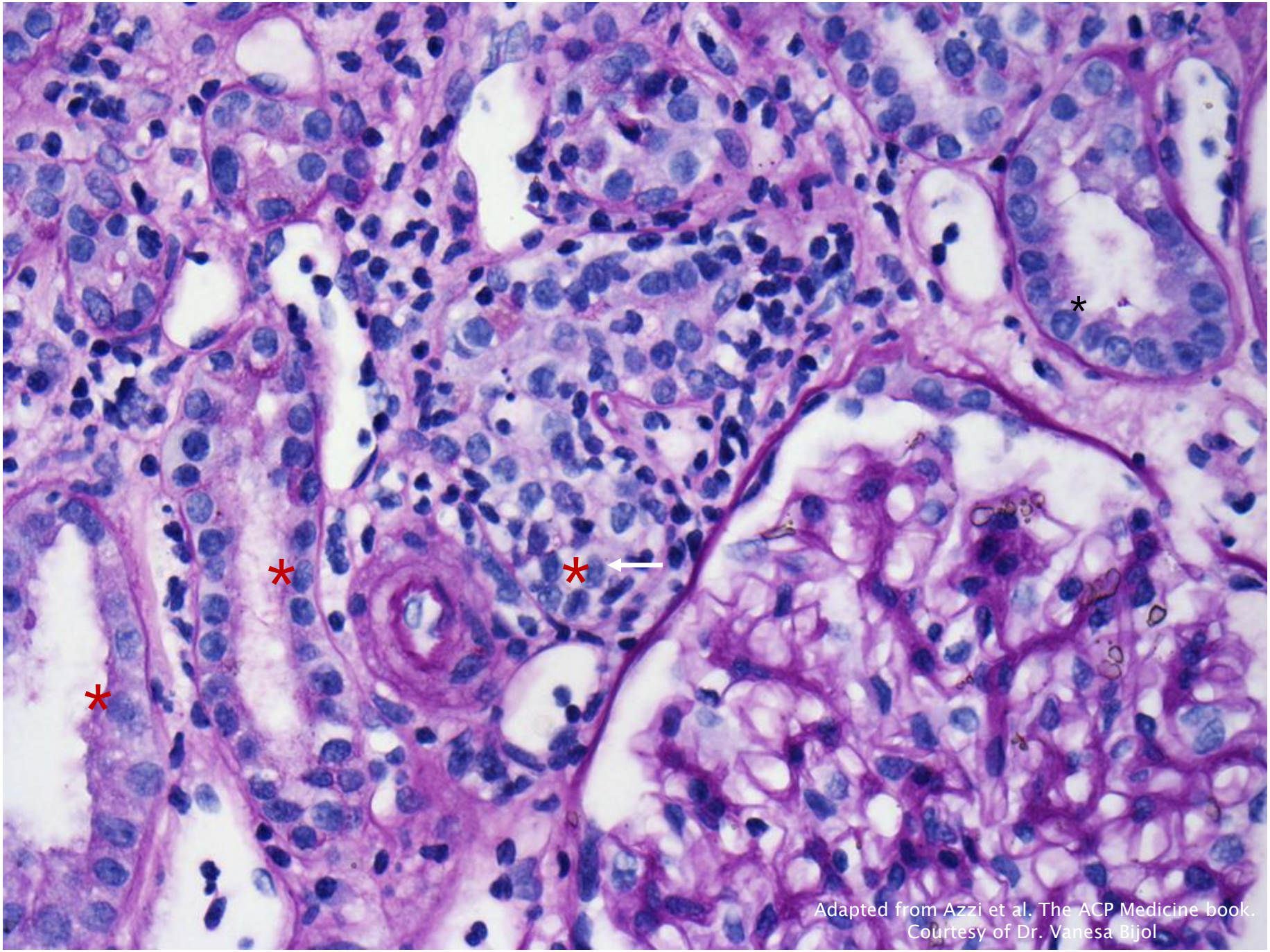
- History:
  - IS, HLA/PRA, induction, nephrotoxic meds, drug interaction

- Transplant specific :
  - Immunologic: Acute rejection (cellular/humoral)
  - Infection: BK nephropathy
  - Drug: Acute CNI toxicity, drug-interaction, CNI induced thrombotic microangiopathy
  - Vascular: Transplant renal artery stenosis

Diagnostic studies

- Renal ultrasound; resistive index: measures vascular impedence
- Protein:creatinine ratio
- CNI level
  - CNI toxicity- acute toxicity is often reversible without any structural damage

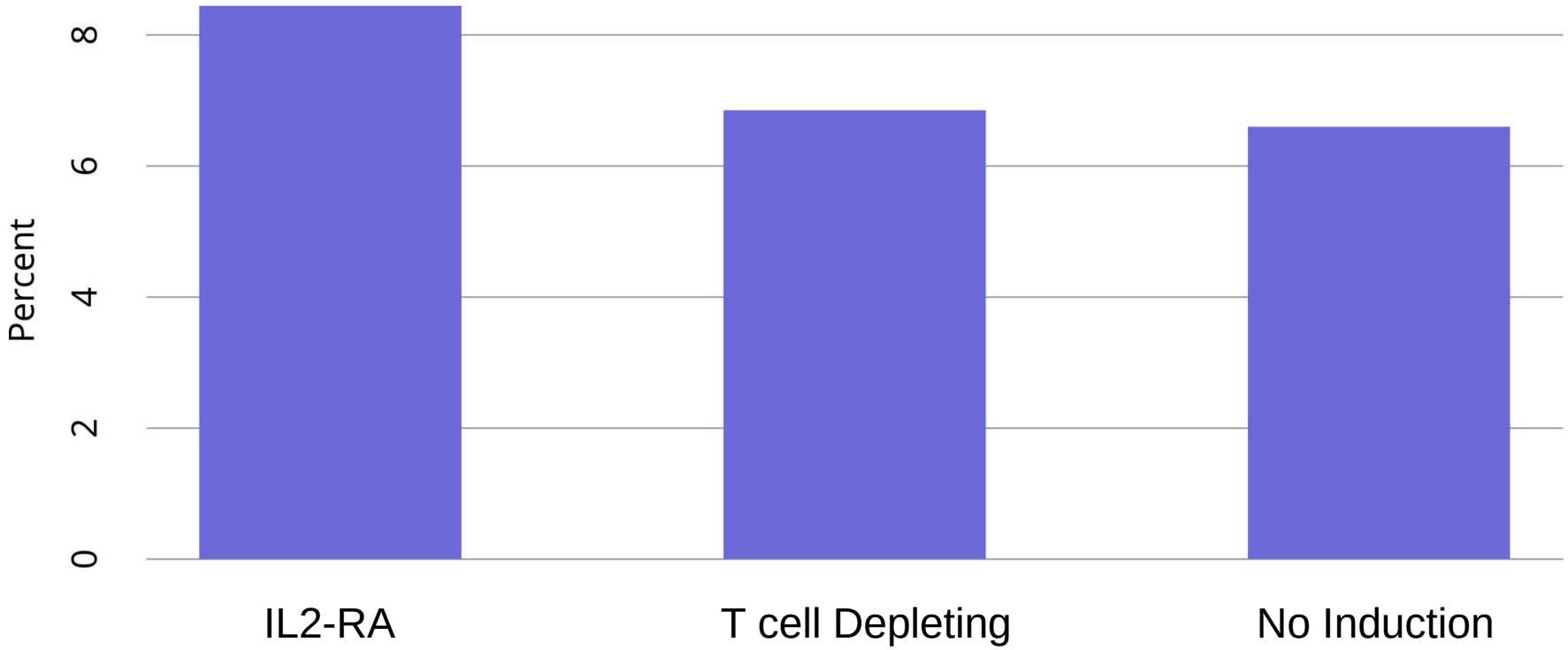
  Other drug interactions:
  - Cytochrome P450 inducer: reduces CNI level and lead to rejection: anticonvulsants, INH, rifampin
  - P450 inhibitors: lead to CNI toxicity: erythromycins, verapamil, diltiazem, antifungals
- Hydration trial
- Transplant biopsy


Adapted from Azzi et al. The ACP Medicine book.
Courtesy of Dr. Vanesa Bijol

Acute rejection

- < 10% in the first year after transplant.
- 75% of acute rejection episodes occur in the first 3 months after transplantation.
- Higher risk:
  - ABO incompatible Tx;
  - Increased number of HLA mismatches
  - Younger recipient and older donor age
  - African-American ethnicity (in the United States)
  - Panel reactive antibody (PRA) greater than 0 percent
  - Presence of a donor-specific antibody (DSA)
  - Blood group incompatibility
  - Delayed onset of graft function
  - Cold ischemia time greater than 24 hours
- Rejections that occur after 3 months post transplant are associated with a worse long term prognosis.

Incidence of acute rejection by 1 year posttransplant among adult kidney transplant recipients by induction agent, 2017-2018.

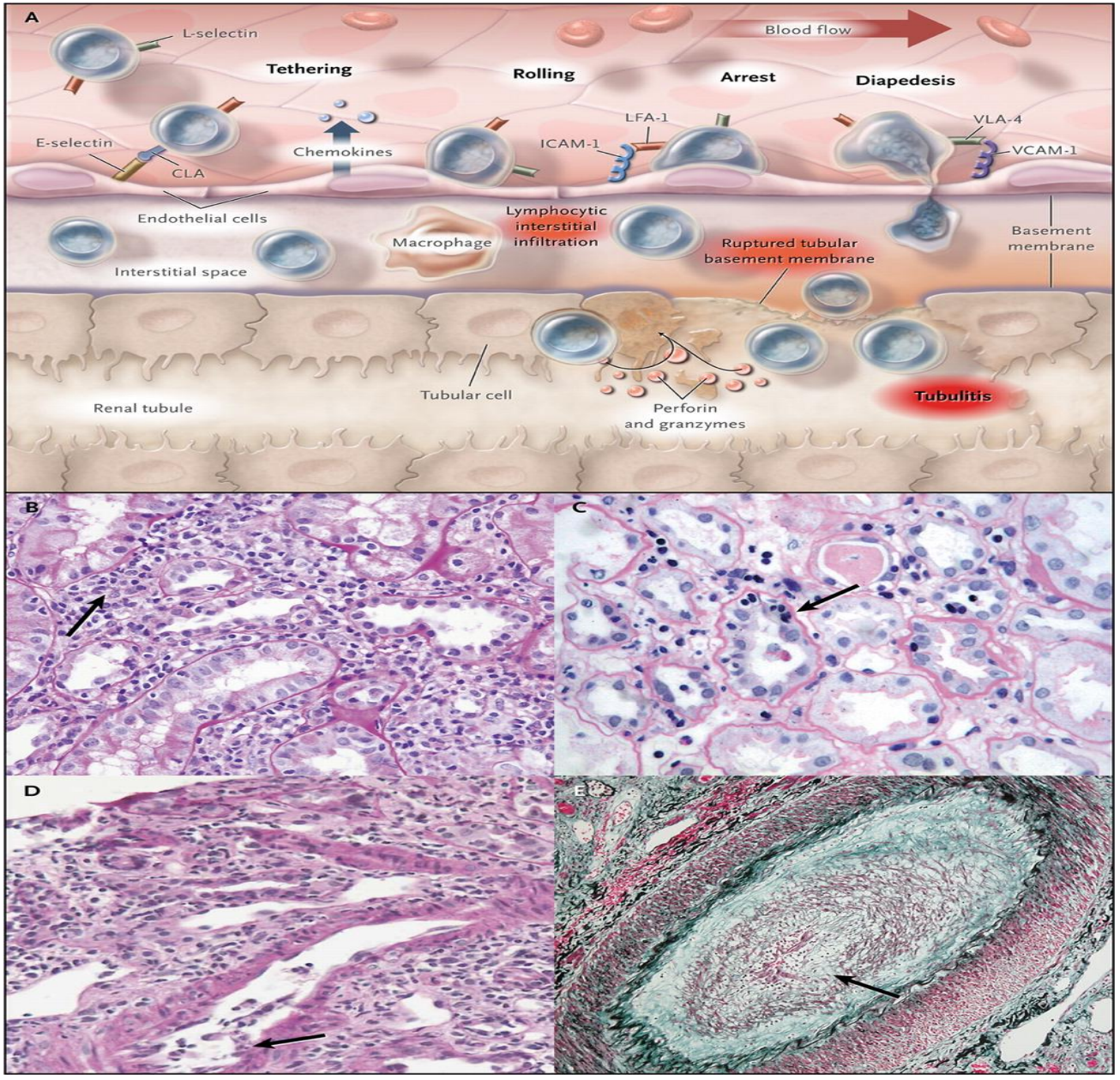


OPTN/SRTR 2019 Annual Data Report: Kidney

American Journal of Transplantation, Volume: 21, Issue: S2, 17 February 2021, DOI:(10.1111/ajt.16502)

Acute T cell-mediated rejection

- **T cell transport into the allograft after activation in the lymphoid organs**
- **T cells invading tubules causing T cell mediated rejection – Tubilitis**
- **Early reversible rejection no impact on long term**
- **Protocol biopsies have shown evidence of 'rejection' with stable kidney function**
- **Cell Free DNA not always elevated with acute rejection**



Acute T cell-mediated rejection

BANFF criteria

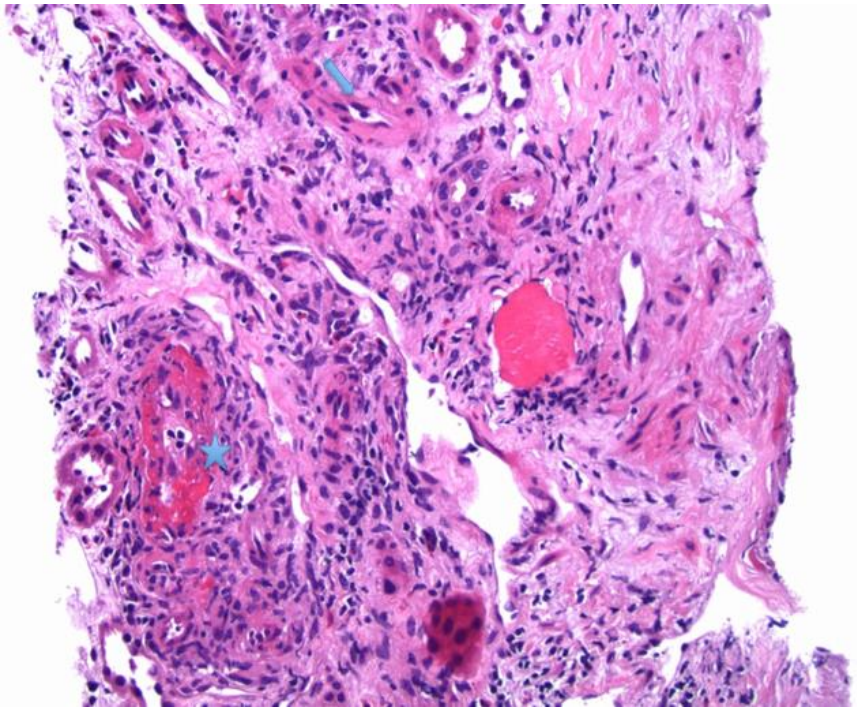
Type IA — Significant interstitial inflammation (>25 percent of parenchyma affected) and moderate tubulitis (>4 cells/section).

Type IB — Significant interstitial inflammation (>25 percent of parenchyma affected) and severe tubulitis (>10 cells/section)

Type IIA — Mild to moderate arteritis found in at least one arterial cross section.

Type IIB — Severe arteritis, which is associated with greater than 25 percent loss of luminal area

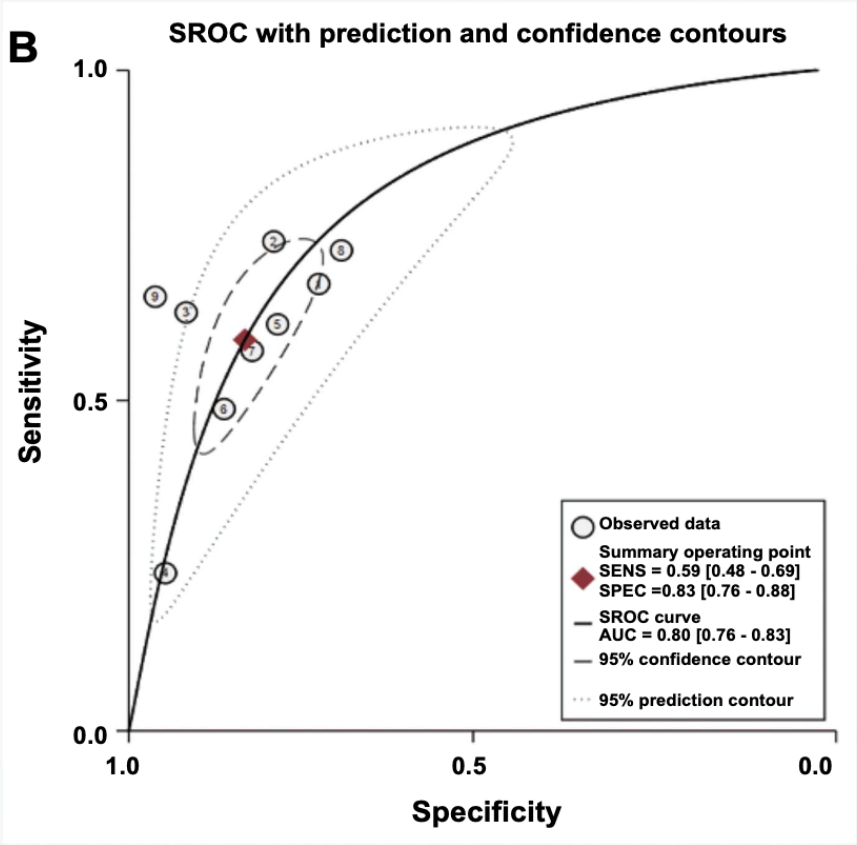
Type III — Transmural arteritis, and/or arterial fibrinoid alterations, and necrosis of medial smooth muscle cells occurring in association with lymphocytic inflammation of the vessel.



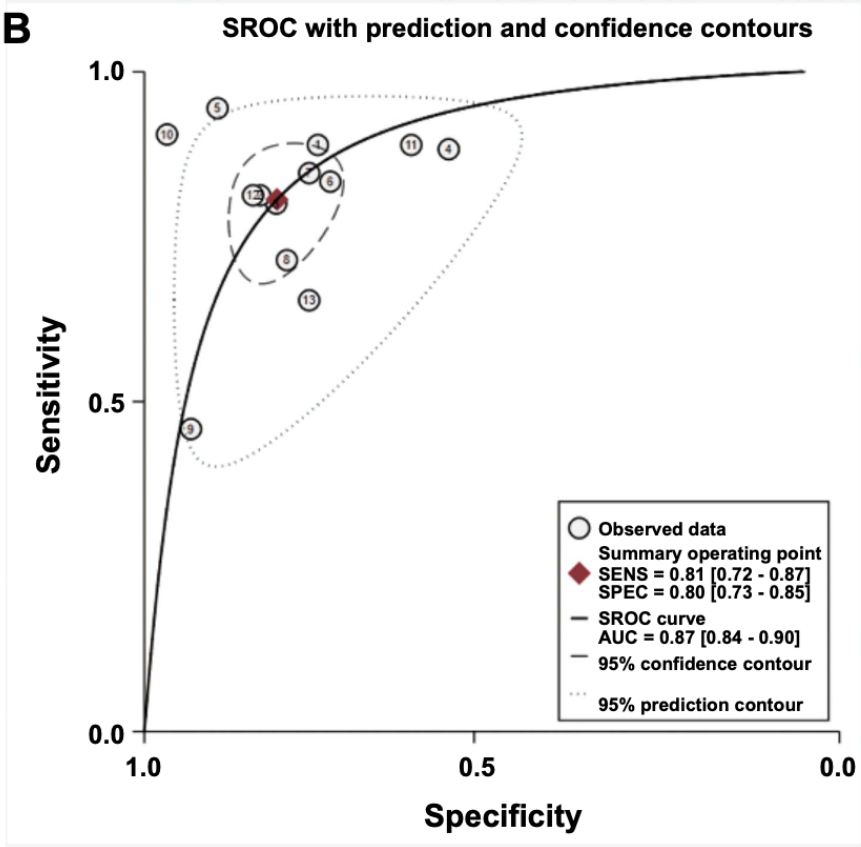
Necrosis indicates BANFF type 3 cellular rejection

sROC with Prediction and Confidence Contours of dd-cfDNA in Acute Kidney Transplant Rejection

Cellular Rejection



Antibody Mediated Rejection



Xing Y, et al Donor-derived cell-free DNA as a diagnostic marker for kidney-allograft rejection: A systematic review and meta-analysis. Biomol Biomed. 2024

Treatment strategies

- Empiric (not recommended) Methylprednisolone 5 mg/kg IV infusion
  - Dose: 3 to 5mg/Kg IVPB (maximum 500 mg) for 3 doses daily + taper
  - If no improvement by 3-5 days – repeat/ re-biopsy/ escalate
- Anti-lymphocytic antibodies:
  - Severe cellular rejection (grade IIA or higher)
  - Thymoglobulin: 1.5 mg/Kg for 3 days, alemtuzemab 30 mg
- Post-episode treatment strategies: reinstitute steroids, switch CNI, add MMF if not part of regimen already.

Webster AC, et al. Monoclonal an polyclonal antibody therapy for treating acute rejection in kidney transplant recipients: a systematic review of randomized trial data. Transplantation 81: 953-965, 2006.

Patient 3

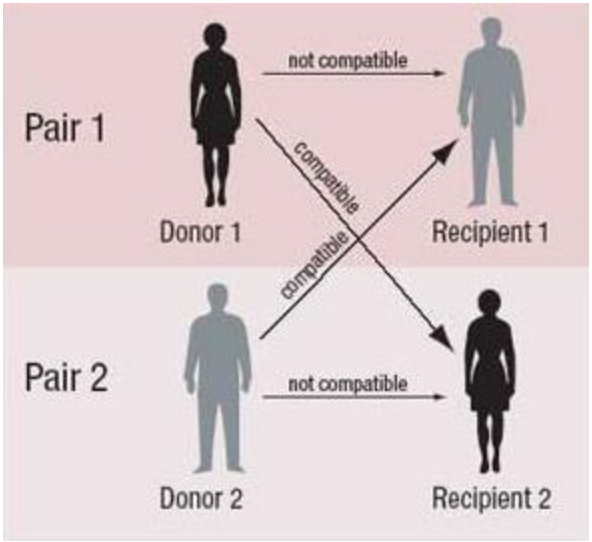
A 40 y/o Caucasian woman with ESRD secondary to lupus nephritis s/p first living related kidney transplant from her husband in 2010 (6 antigen mismatch) lost due to ABMR in 2011.

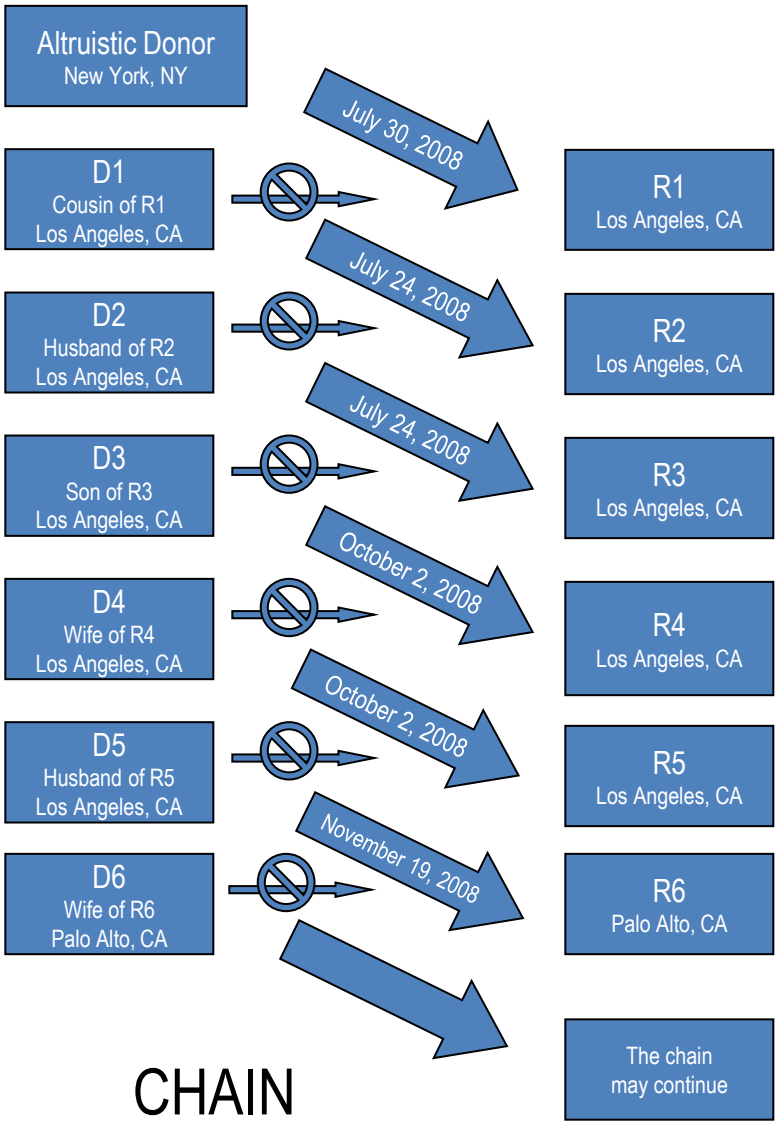
- No other medical history.
- She was on PD for the last 2 years.
- Her cPRA is Class I is 99% and Class II is 87%.
- She was evaluated for LURT from her brother in law HLA MM is A2B2DR2.
- T cell crossmatch positive.
- + Donor Specific Antigan against HLA-A66

How should the patient be managed?

Paired Donation

SWAP



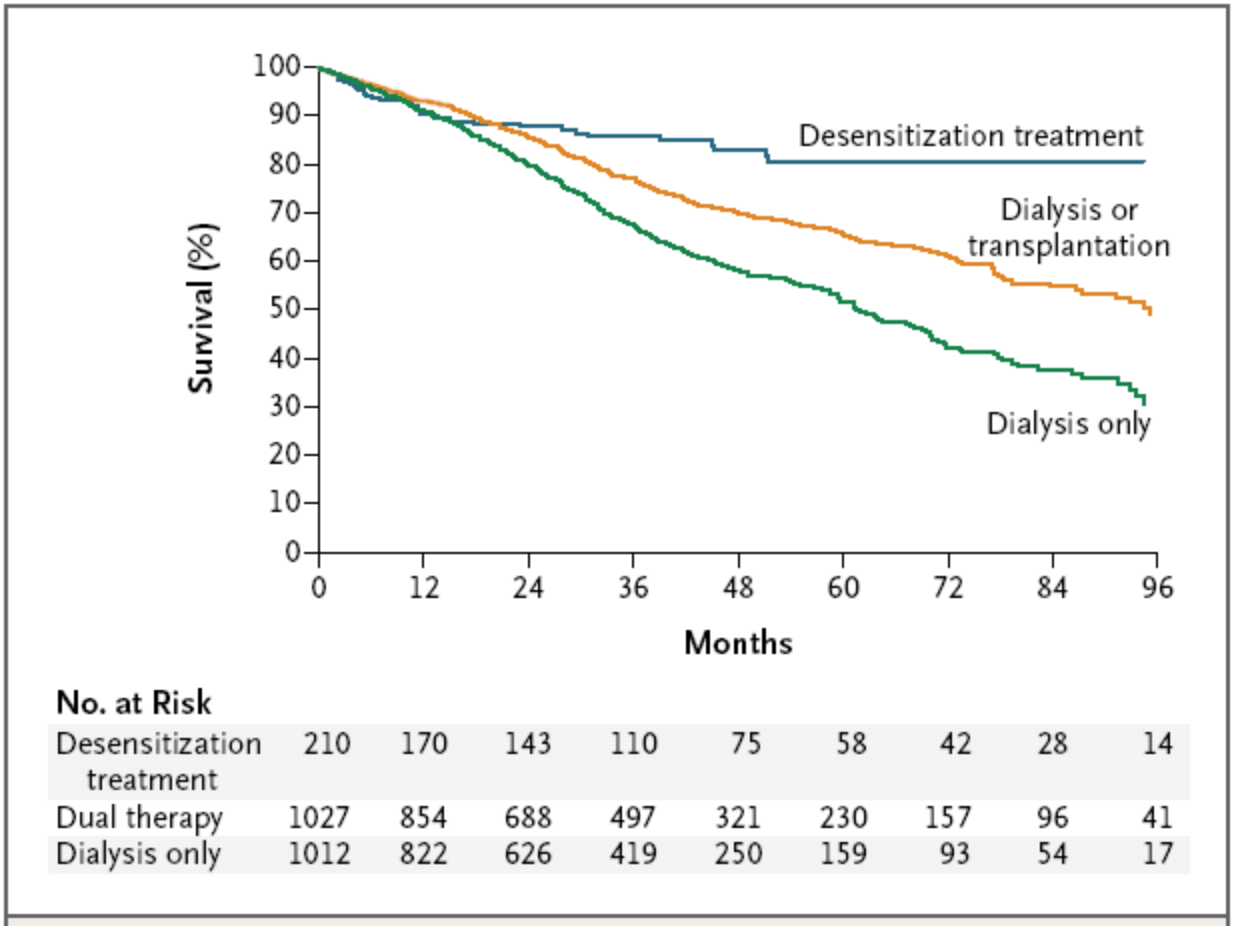


CHAIN

Desensitization in HLA-Incompatible Kidney Recipients and Survival

Robert A. Montgomery, M.D., D.Phil., Bonnie E. Lonze, M.D., Ph.D., Karen E. King, M.D., Edward S. Kraus, M.D., Lauren M. Kucirka, Sc.M., Jayme E. Locke, M.D., M.P.H., Daniel S. Warren, Ph.D., Christopher E. Simpkins, M.D., M.P.H., Nabil N. Dagher, M.D., Andrew L. Singer, M.D., Ph.D., Andrea A. Zachary, Ph.D., and Dorry L. Segev, M.D., Ph.D.

- 211 highly sensitized patients who underwent live donor transplant
- Treated with PP/low dose IVIG
- Desensitization with live donor provided significant survival benefit as compared with waiting for compatible organ



No. at Risk

Desensitization treatment	210	170	143	110	75	58	42	28	14
Dual therapy	1027	854	688	497	321	230	157	96	41
Dialysis only	1012	822	626	419	250	159	93	54	17

Available Strategies for DSA removal

- **Removal of Antibodies by Plasmapheresis**
  - PP is not specific for Ig removal
  - Anti-HLA antibody titer rebounds
- **Inhibition of Antibody production**
  - **Rituximab (Anti-CD20):**
    - Pre-B and mature B lymphocytes
    - Plasma cell do not express CD20
  - **Bortezomib (proteasome inhibitor):**
    - Induce apoptosis of plasma cells
- **Inactivation of Ab**
  - **Complement inhibition**
  - **Imlifidase**
  - **IL-6 antibodies**

Available Strategies for DSA removal

- **Intravenous Ig:**
  - Neutralization of circulating anti-HLA antibodies through anti-idiotypic antibodies.
  - Bind C3b and C4b and neutralize C3a and C5a
  - binding to Fc receptors
- **Splenectomy:**
  - Major source of Lymphocyte including B cells and plasma cells

Patient 3

Patient was desensitized

- 5 sessions of PP followed with 10gms of IVIG.
- FK 2mg BID and MMF 1gm BID.
- DSA titers were reduced by more than 70%.
- Repeated CDC CX was negative.

Patient was then induced with Thymo 1.3 mg/kg x 4 daily doses and continued on FK, MMF with steroid taper. Also got Rituximab 375 mg/m^2.

Transplantation was uneventful with urine output of 200-300cc/hr.

Creatinine post op

day 0 - 7.2

day 1 - 4.2

day 7 - 1.7

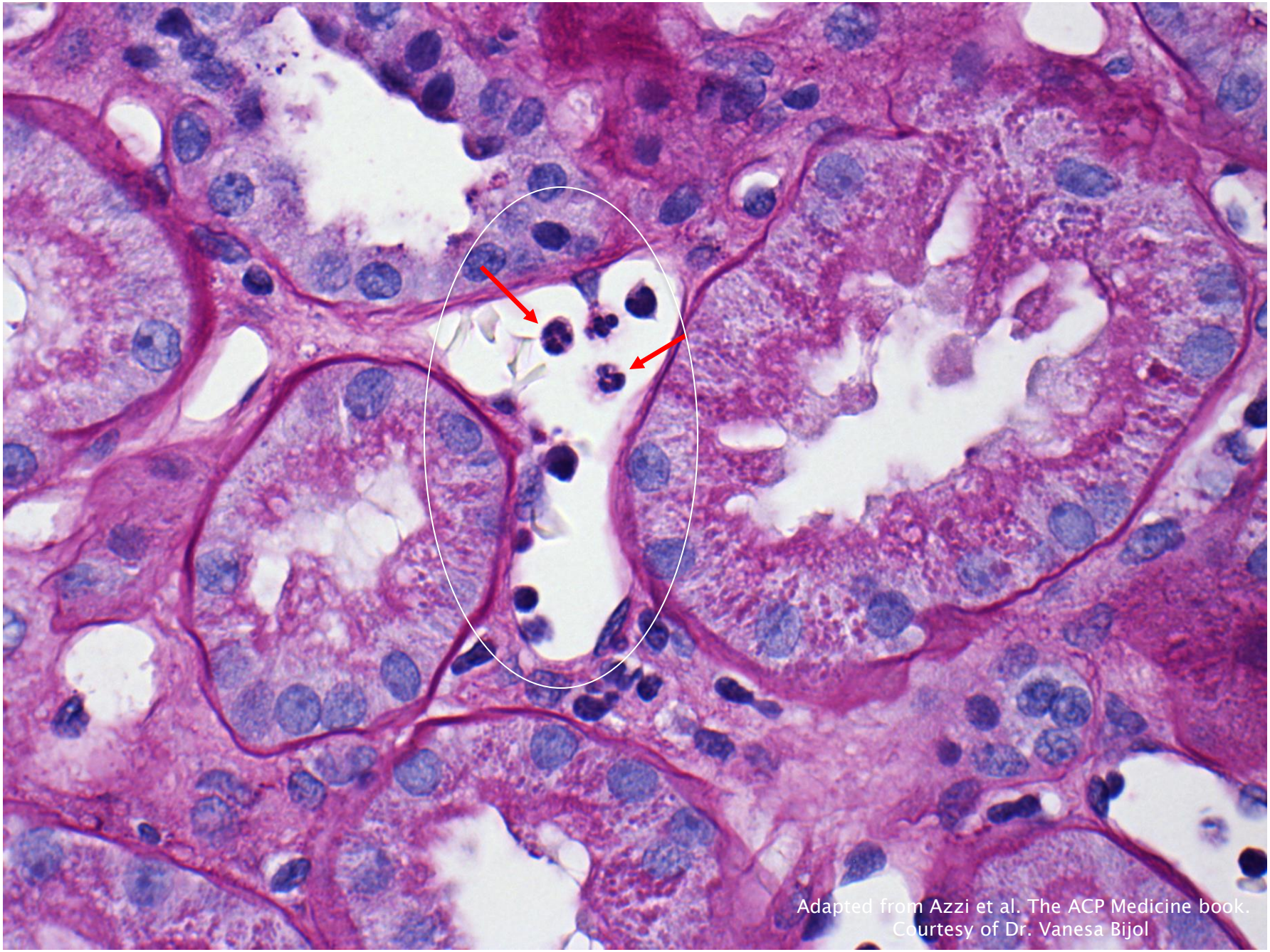
day 10 - 2.4

What would a biopsy likely show?

Antibody Mediated Rejection

	Early acute ABMR (+XM)	Acute ABMR	Active (smoldering) ABMR	Chronic active ABMR
Clinical setting	Clinically apparent: AKI, <1 month post-transplant	Usually clinically apparent: AKI	Subclinical	Subclinical or clinically apparent: Progressive renal insufficiency, proteinuria, hypertension
Histology	ATN, thrombi, mild capillaritis, v lesions	ATN, thrombi, capillaritis, v lesions	Capillaritis only (g, ptc)	Capillaritis and TG, TA, or PTCBMML
C4d	Diffuse +	+	Negative, focal +, occasionally diffuse +	Negative, focal +, occasionally diffuse +
Serum DSA	High	High	Low, mid	Low, mid

Cornell LD. Histopathologic Features of Antibody Mediated Rejection: The Banff Classification and Beyond. Front Immunol. 2021 Sep 27;12:718122


Adapted from Azzi et al. The ACP Medicine book.
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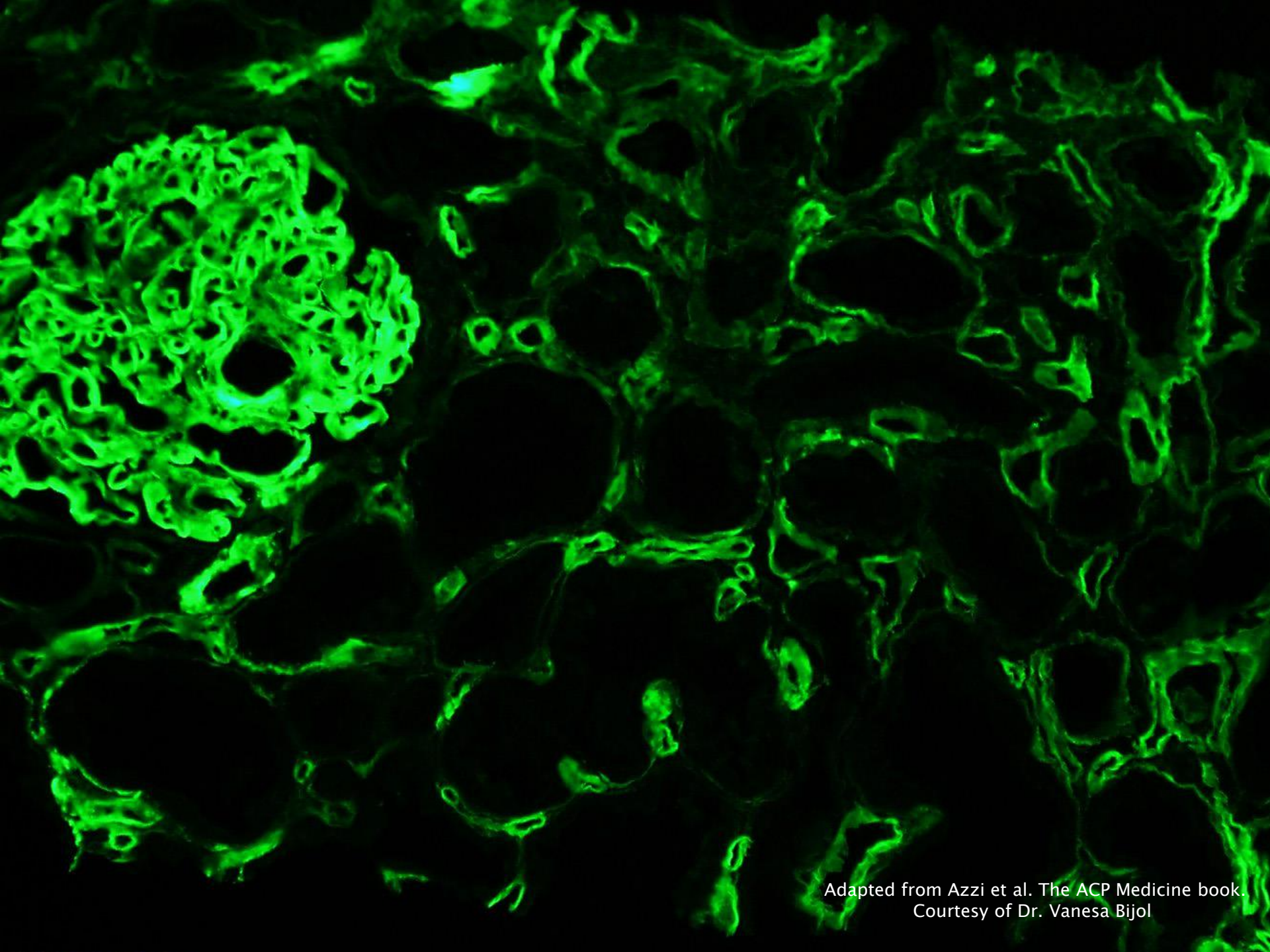
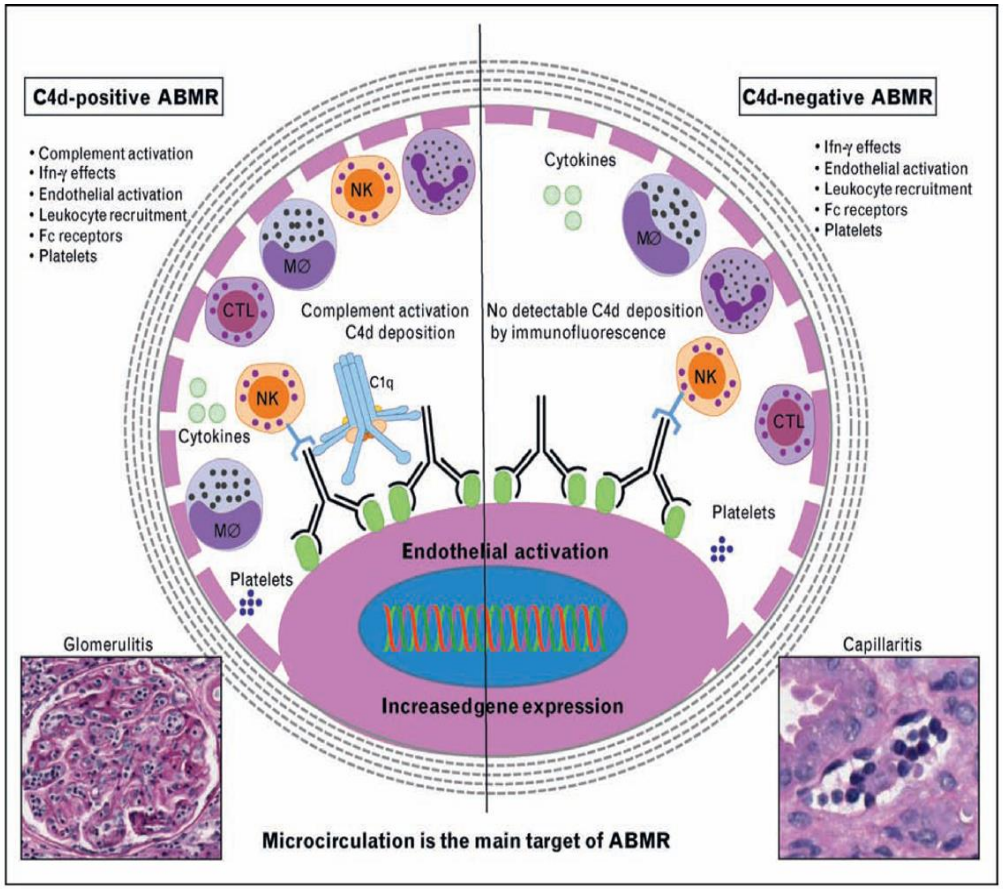


Adapted from Azzi et al. The ACP Medicine book.
Courtesy of Dr. Vanesa Bijol

Acute antibody-mediated rejection (AMR)

- The central feature is endothelial injury within the microvasculature.
- Risk factors for AMR:
  - Elevated PRA
  - Prior transplantation
  - Historically positive crossmatch,
  - Female sex.
  - No correlation with HLA match
  - Ischemic time, or donor characteristics.



Microcirculation inflammation (peritubular capillaritis and glomerulitis; bottom microscopic pictures) and damage (multilayering of basement membrane – dashed lines in the schematic capillary figure – and/or glomerular double contours, transplant glomerulopathy) are the typical histological lesions in allografts exposed to antibody-mediated injury (periodic acid–Schiff reagent staining, original magnification ×400). ABMR, antibody-mediated rejection; CTL, cytotoxic T lymphocytes; Mø, monocytes–macrophages; IFN-γ, interferon-gamma; NK, natural killer.

Clinical criteria of diagnosis of acute AMR

Morphologic evidence of tissue injury:

- **Type I: ATN-like histology with minimal inflammation**
- **Type II: capillary glomerulitis with margination and/or thrombosis**
- **Type III: arterial-transmural inflammation/fibrinoid changes**

Immunopathologic evidence for antibody mediated action:

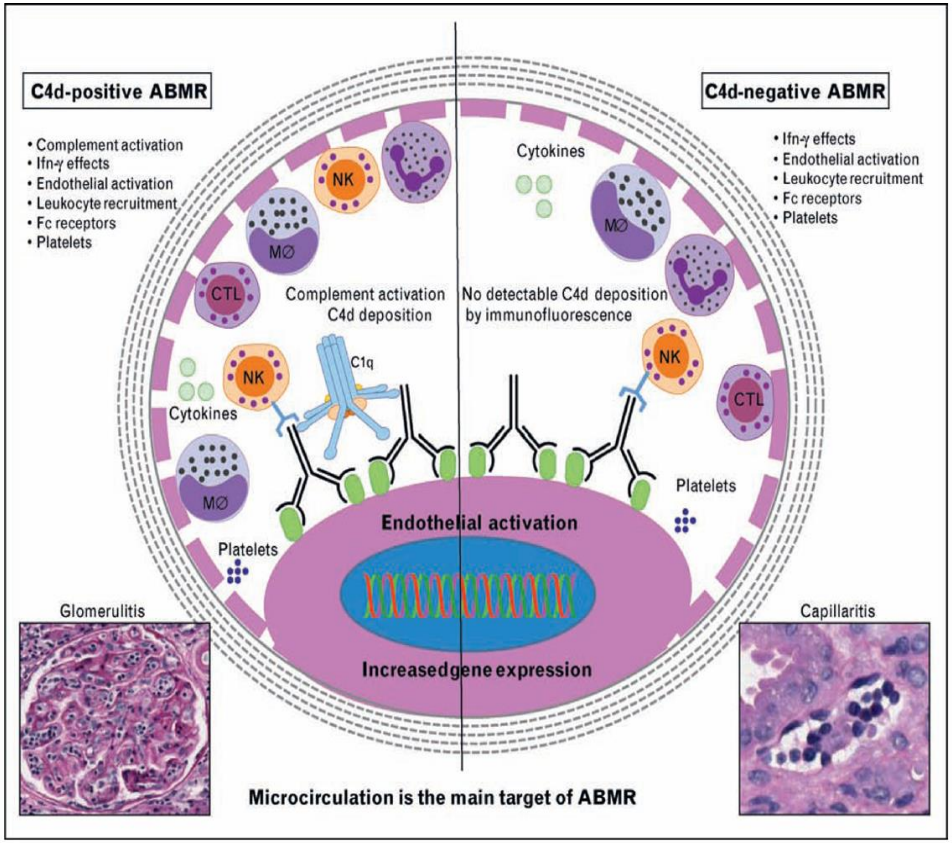
- **C4d deposition of the peritubular capillaries that can be diffuse or focal**

Serologic evidence for circulating antibodies to

- **Donor HLA**
- **Donor endothelial antigens.**

***Chronic* antibody-mediated rejection:**

- **Morphologic features of transplant glomerulopathy,**
- **C4d deposition in proximal tubular cells**
- **Presence of DSA**



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Incidence and Prognosis of AMR

- Antibody mediated rejection resulting in graft dysfunction is estimated to occur in **3 to 10 % of high risk renal transplants**
- In general: antibody-mediated immunologic processes portend **a worse prognosis**
- In addition- recent studies suggest that chronic immune injury mediated by anti-donor antibodies may account for the **majority of graft losses**

Treatment for AMR

- First line: Plasmapheresis and IVIG
  - Plasmapheresis:

    40-60 cc/kg fluid replacement :1/3 Isotonic fluid, 2/3 Albumin

    FFP replace albumin in the second treatment, sometimes in the first treatment if starting pheresis within 3 days of the biopsy or surgery.
  - IVIG:

    10 gms after each pheresis
- Second line: Cincinnati protocol: PP, IVIG, Rituximab and Bortezomib
- Third line: Anti complement inhibitor
  - Initial dose: 1200 mg x 1
  - Subsequent doses: 600 - 900 mg given at weekly intervals.
  - Total course of therapy: the manufacturer recommends the administration of 8 doses, but the patient should be re-assessed following the initial 4 doses and a decision should then be made about continuation of therapy.
  - Prophylaxis
    - Trimethoprim-Sulfamethoxazole160/800 mg po daily, penicillin vk 500 mg po twice daily or levofloxacin 500 mg po daily

Treatment of AMR

Agent	Dosing	MOA	Adverse Events	Cost
IVIG	• Low-dose after PP (10-100 g) • High-dose alone (2 g/kg)	• Neutralizes circulating autoantibodies • Promotes down-regulation of antibody production	• Infusion-related reactions • Mental status changes • Renal dysfunction	• 10 g = $1358.28 • 2 g/kg = $19,015.92
Rituximab	• 375 mg/m^2 • 1000 mg	• Anti-CD20 monoclonal antibody that induces B-cell destruction through complement dependent cytotoxicity	• Infusion-related reactions • Infection • Mucocutaneous reactions (i.e., SJS) • Myelosuppression	• 375 mg/m^2 (1.73 m^2) = $5,190.00 • 1000 mg = $8,000.00
Bortezomib	• 1.3 mg/m^2 on Days 1, 4, 7, 10	• Proteasome inhibitor that induces cell-cycle arrest and apoptosis of plasma cells	• Myelosuppression • Neuromuscular (neuropathy, myalgias)	• One cycle (4 doses) = $4,762.20
Eculizumab	• 1200 mg x 1 • 900 mg weekly x 4 doses • 1200 mg at week 5	• monoclonal antibody that inhibits its cleavage of C5 to C5a and C5b, thus preventing the generation of the MAC	• Infection (risk for meningococcal infection – REMS)	• 1200 mg = $27,324.00

Kim, et al. Pharmacotherapy 2014;34(7):733-44

Treatment for Antibody Mediated Rejection

Treatment	Mechanism	Approval Status (U.S.)
Plasmapheresis	Removes DSAs	Standard use; not FDA-approved for AMR
IVIG	Immunomodulation	FDA-approved (not for AMR)
Rituximab	B-cell depletion	Off-label
Bortezomib	Plasma cell depletion	Off-label
Eculizumab	Complement inhibition	Off-label for AMR
Tocilizumab	IL-6 pathway inhibition	Off-label
Imlifidase (IdeS)	IgG cleavage	EU-approved (desensitization); under study in U.S.

Experimental Agents for Treatment of AMR

Agent	Target	Stage	Notes
Imlifidase	IgG degradation	Phase 3 (US)	EU-approved for desensitization
Felzartamab	CD38 (plasma cells)	Early-phase trial	M-PLACE study
Clazakizumab	IL-6	Phase 3	IMAGINE trial for chronic AMR
Daratumumab	CD38	Case series	Used off-label
Belatacept	Co-stimulation	Investigational	Also used in maintenance
C1-INH	Complement	Case reports	Not routinely used
Inebilizumab	CD19	Preclinical	More potent B-cell depletion
CAR-T	CD19/BCMA	Preclinical	Experimental

Summary

- The choice of induction and maintenance therapy depends on donor and recipient characteristics.
- Delayed Graft function is an acute kidney injury in transplanted kidney and should be worked up accordingly (Pre-renal, Renal, Post-renal)
- Prolonged ischemia time increases risk for DGF but also for acute rejection
- Antibody mediated rejection portends a worse prognosis and may account for the majority of graft losses
- Antibody mediated rejection can occur in the absence of C4d staining and DSA.

Thank you for your attention

Anil Chandraker MD FASN FAST FRCP