Transplantation

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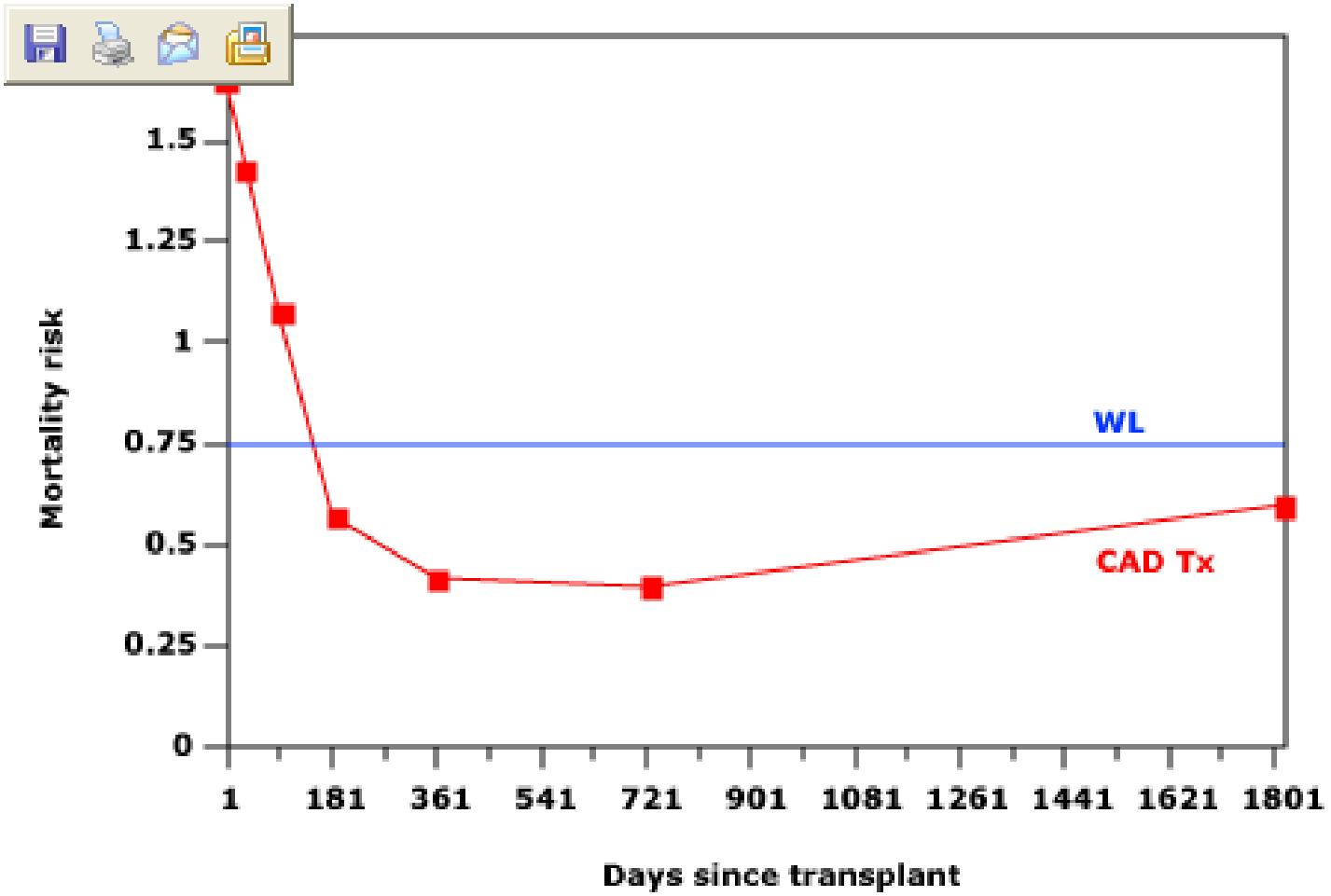
Question 1:

You have been on dialysis for 3 years. A cadaver transplant is offered to you. Do you accept?

A. No, because I'm used to dialysis now
B. Yes, because I dislike dialysis
C. Yes, because I'll live longer

Mortality risk of recipients of cadaveric renal transplants vs. wait-listed patients with ESRD who were on dialysis for at least 2 years



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Question 2:

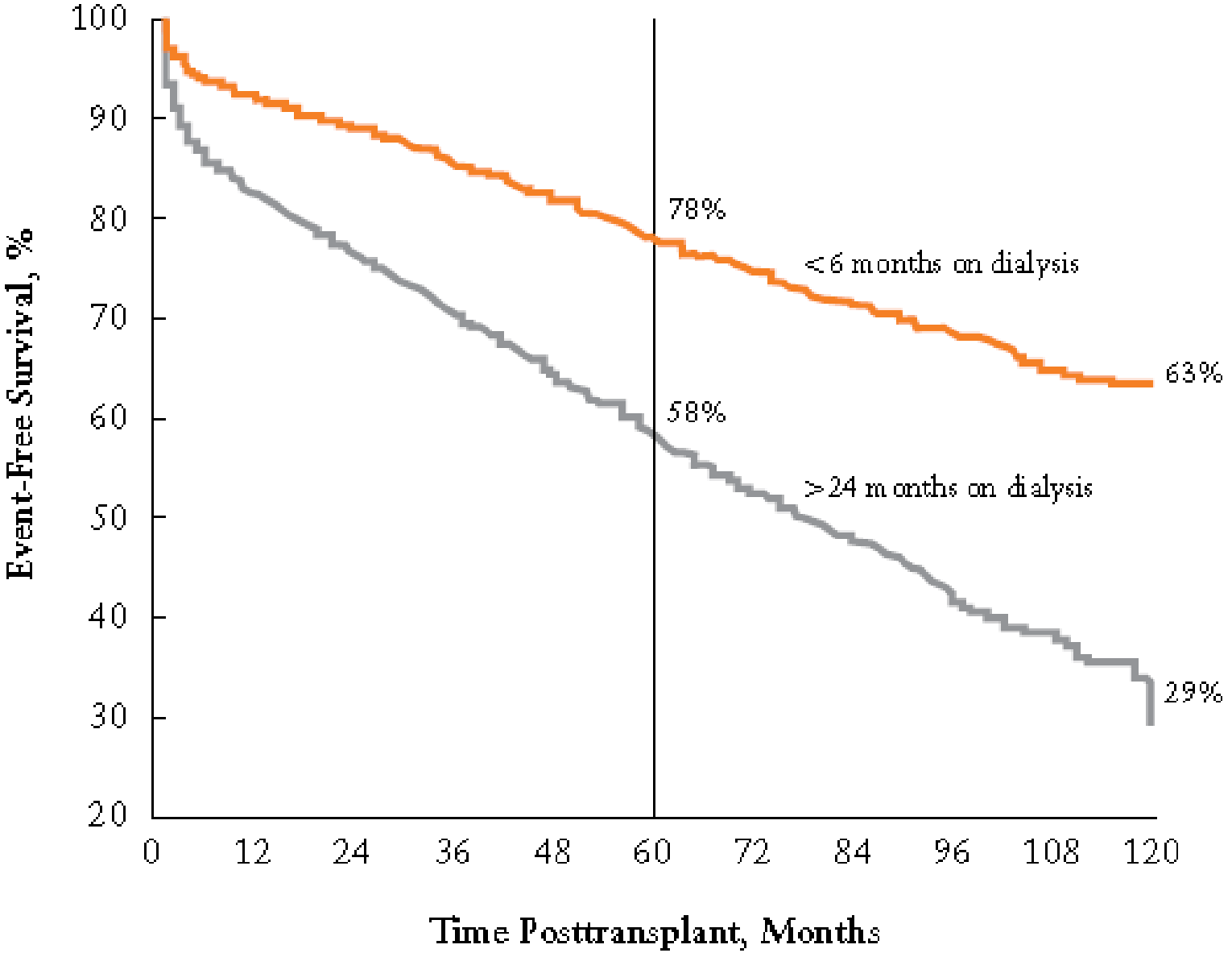
If you were getting a transplant, at what point would you like to get it?

A. Before I start dialysis

B. HD x 6 months

C. HD x 1 year

D. HD x 5 year



Reprinted with permission from Meier-Kriesche HU, Kaplan B. Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes: a paired donor kidney analysis. *Transplantation*. 2002;74:1377-1381.

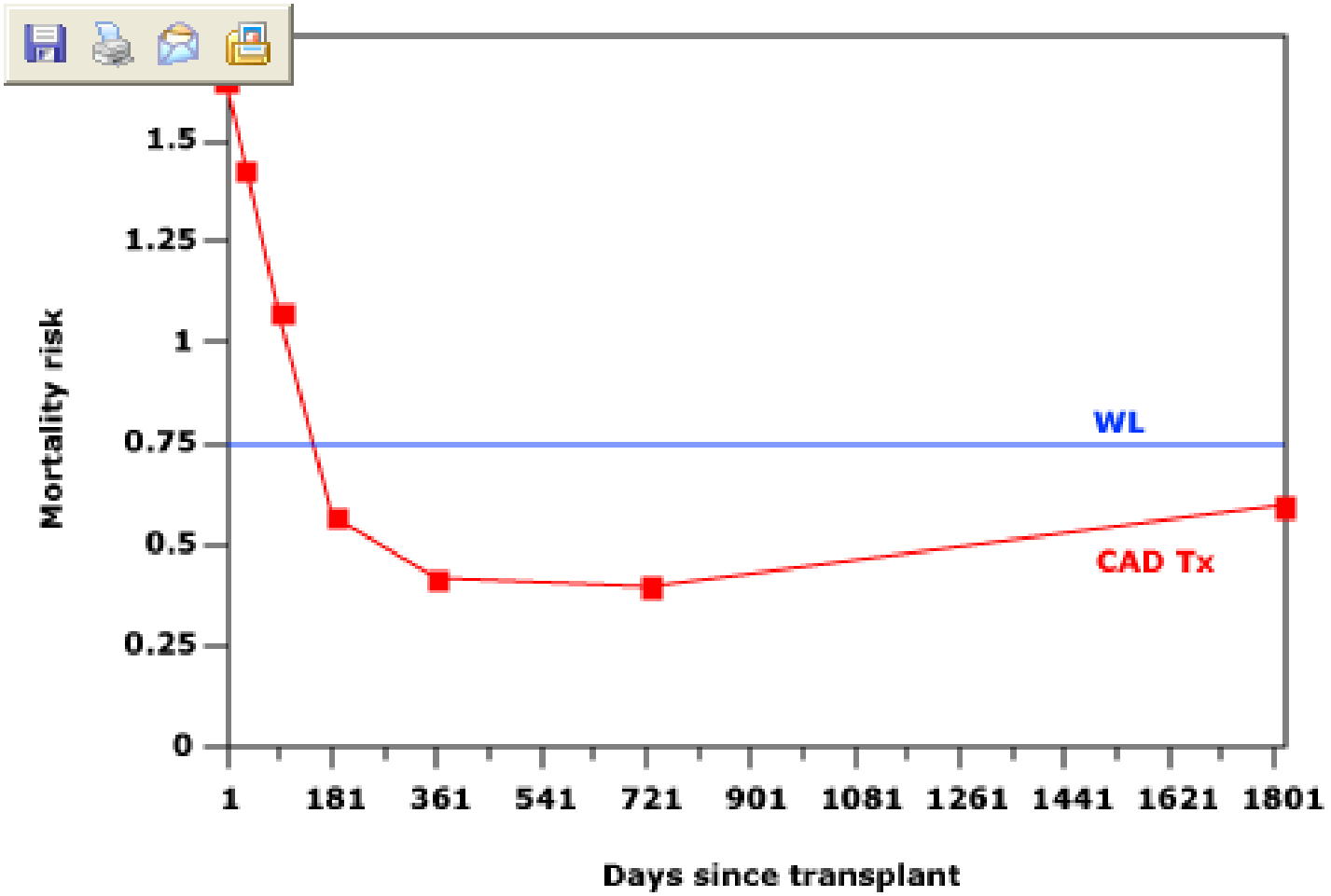
Question 3.

If your life expectancy was 6 months, and you were offered a transplant, would you accept?

A. Yes

B. No

Mortality risk of recipients of cadaveric renal transplants vs. wait-listed patients with ESRD who were on dialysis for at least 2 years



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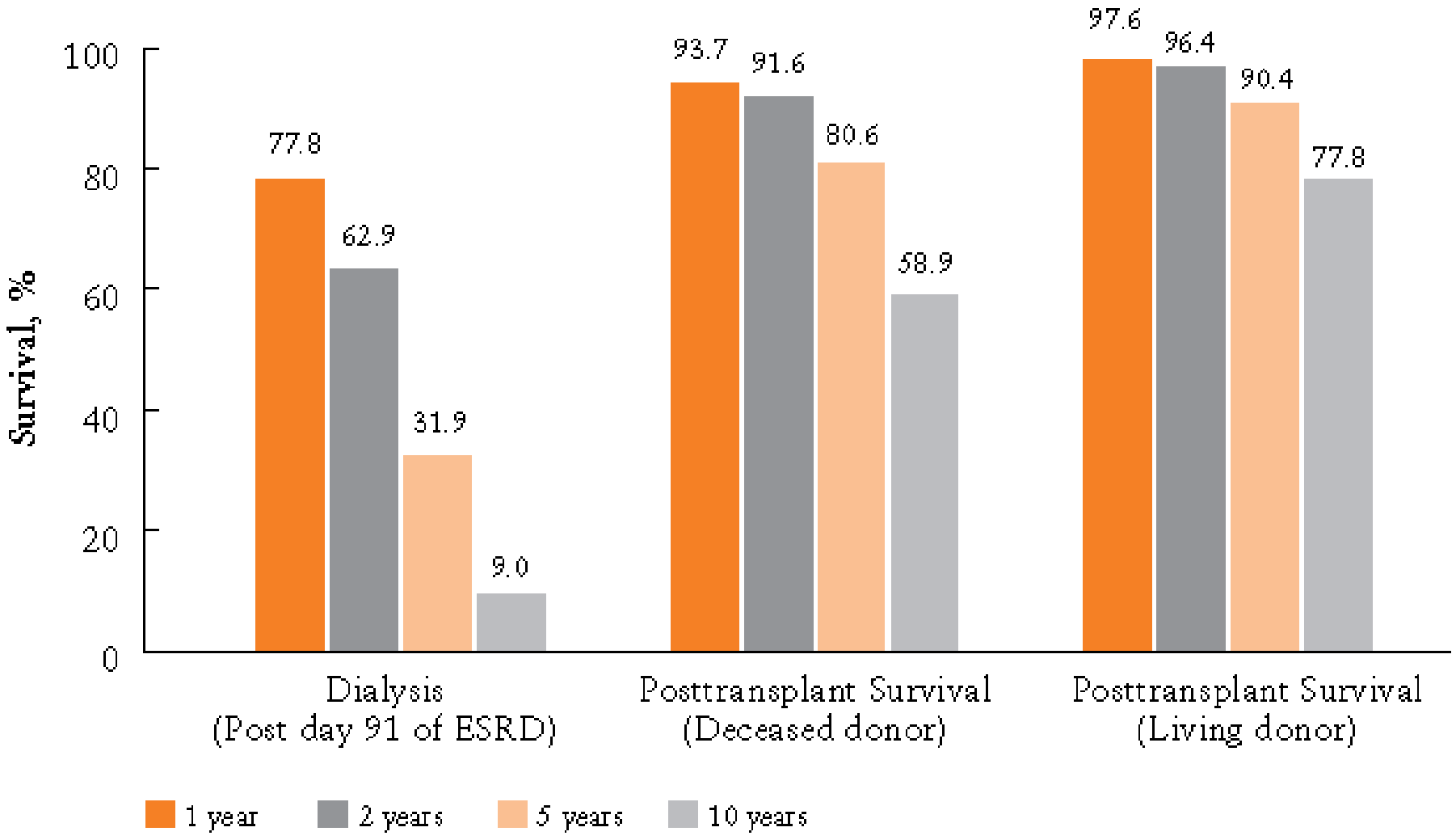
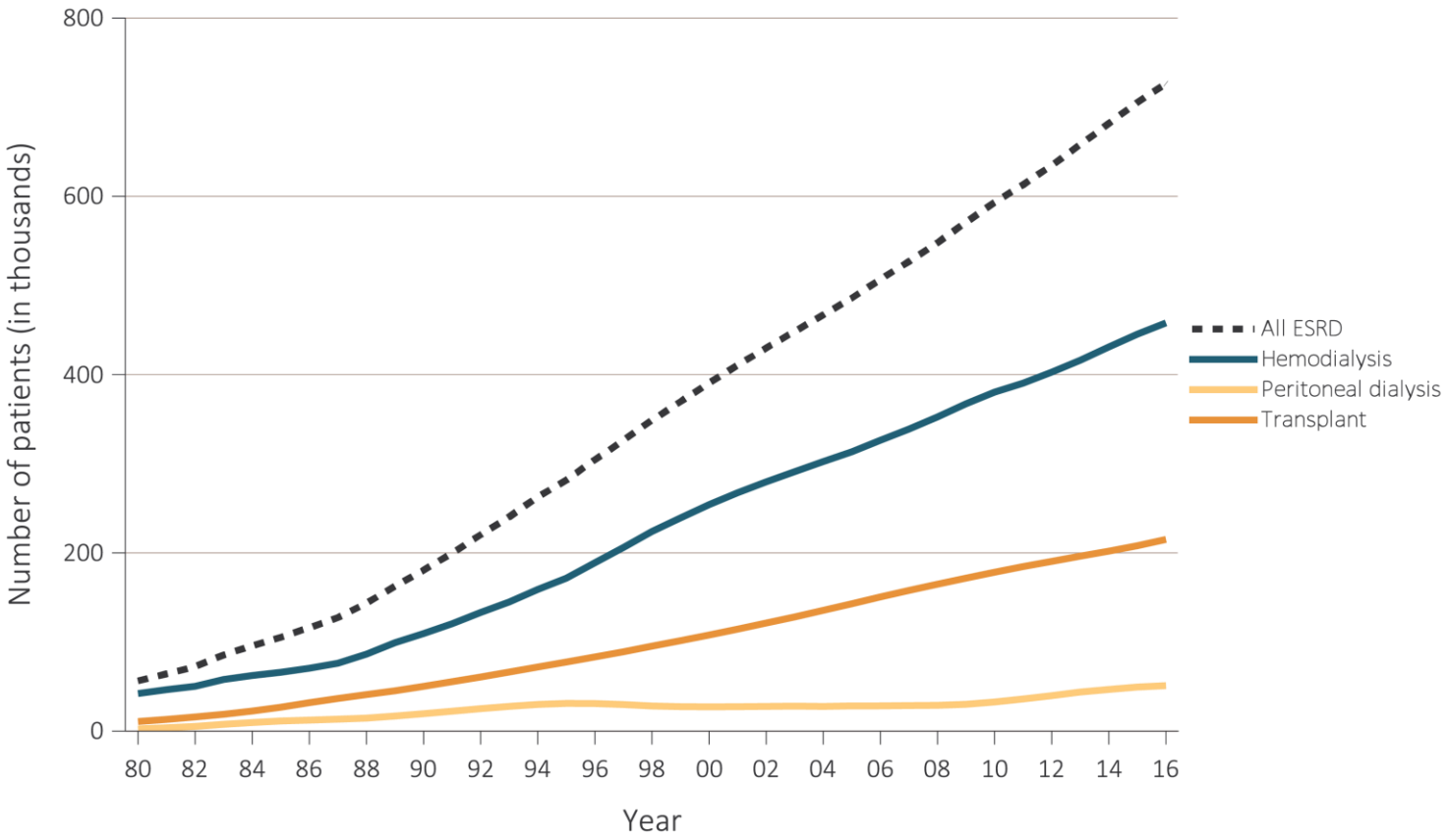
Question 4.

If you were given the option between taking a living donor kidney versus a deceased donor kidney, which one would you pick?

A. Living donor
B. Deceased donor
C. Doesn’t matter
D. Dialysis


Survival, %
100
80
60
40
20
0
77.8
62.9
31.9
9.0
93.7
91.6
80.6
58.9
97.6
96.4
90.4
77.8
Dialysis
(Post day 91 of ESRD)
Posttransplant Survival
(Deceased donor)
Posttransplant Survival
(Living donor)
1 year
2 years
5 years
10 years

Trends in the number of ESRD prevalent cases, by modality, in the U.S. population, 1980-2016



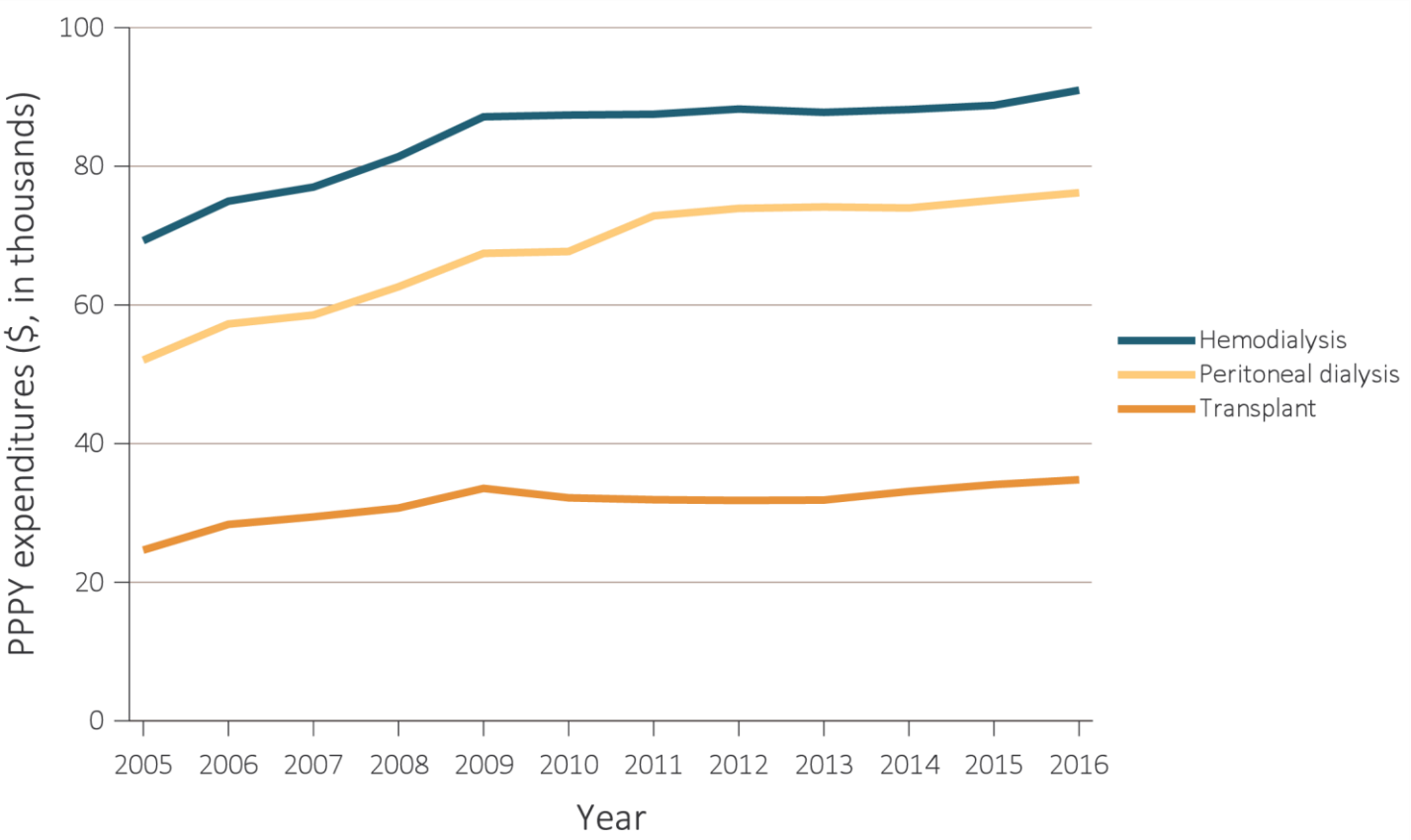
Data Source: Reference Table D1 and special analyses, USRDS ESRD Database. Abbreviation: ESRD, end-stage renal disease. Persons with "Uncertain Dialysis" were included in the "All ESRD" total, but are not represented separately.

Question 5.

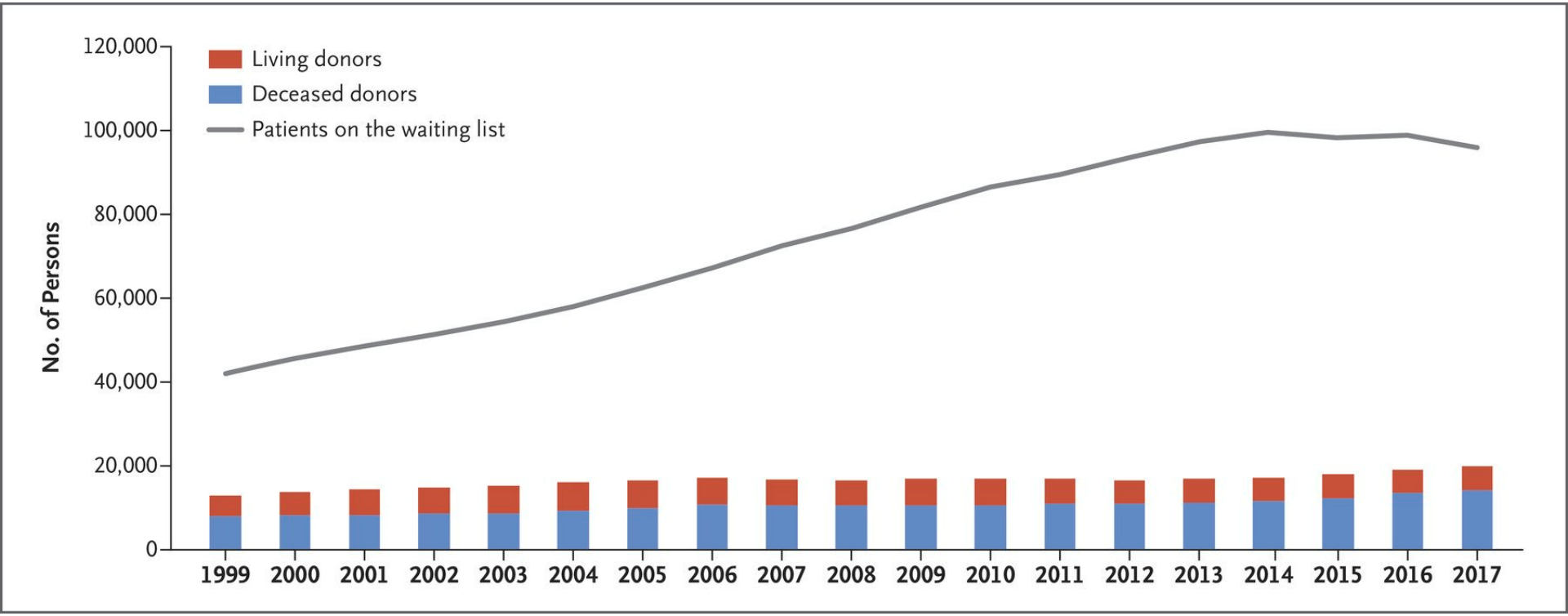
The average annual total (medicare) expenditure for an HD patient is 90K. What's the average annual expenditure for a transplant patient?

A. 100K
B. 75K
C. 50K
D. 35K
E. 10K

Total Medicare ESRD expenditures per person per year, by modality, 2004-2016



Data Source: USRDS ESRD Database; Reference Tables K.7, K.8, & K.9. Period prevalent ESRD patients; includes all claims with Medicare as primary payer only. Abbreviations: ESRD, end-stage renal disease; PPPY, per person per year.

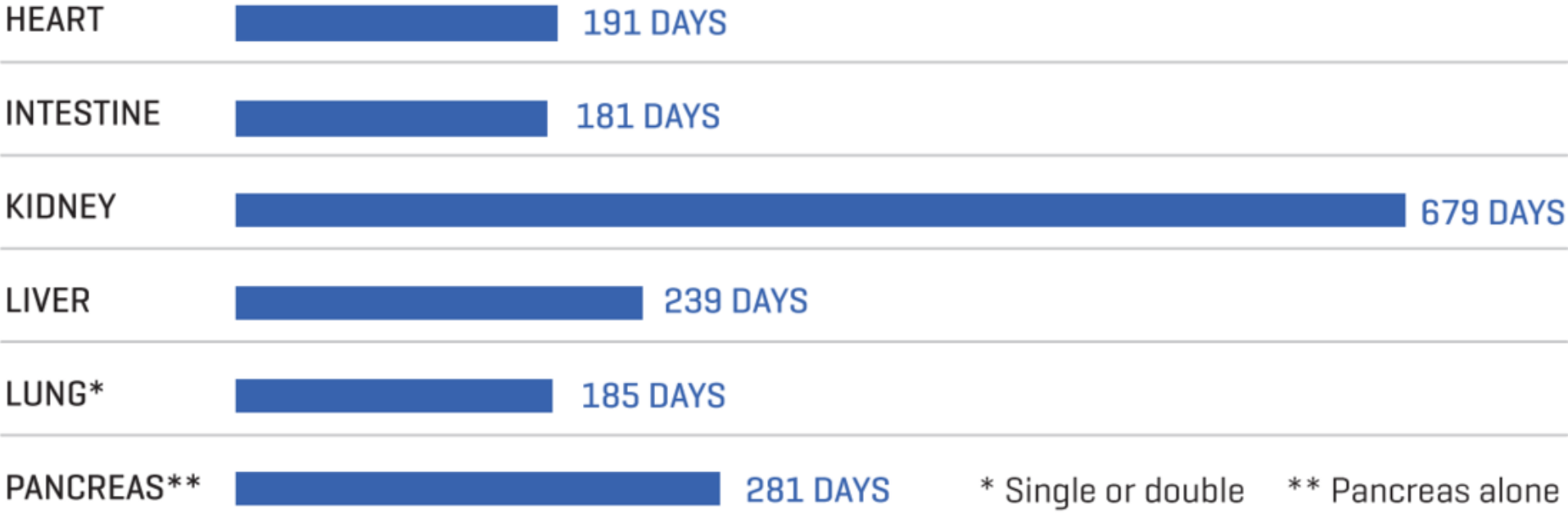

Living donors
Deceased donors
Patients on the waiting list
No. of Persons
120,000
100,000
80,000
60,000
40,000
20,000
0
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017

Question 6.

Which organ has the longest wait time?

A. Liver
B. Heart
C. Lung
D. Kidney

AVERAGE WAITING TIMES FOR ORGANS



SOURCE: MILLIMAN, PROJECTED 2017 NUMBERS

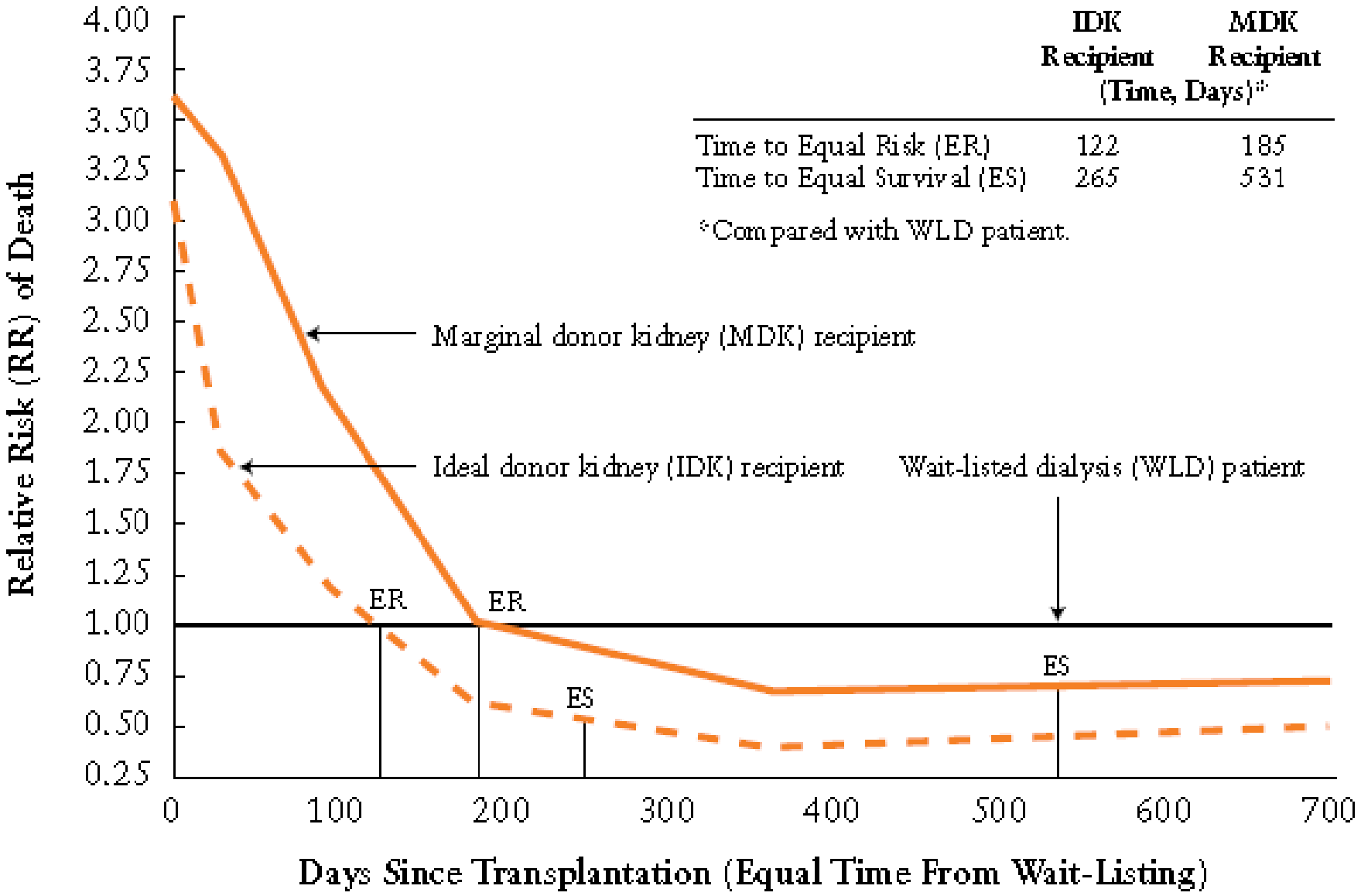
Extended Criteria Donors (ECD)

- Age > 60
- Age 50-59 + 2 of the following
  - Cr > 1.5
  - HTN
  - Cerebrovascular death

Question 7.

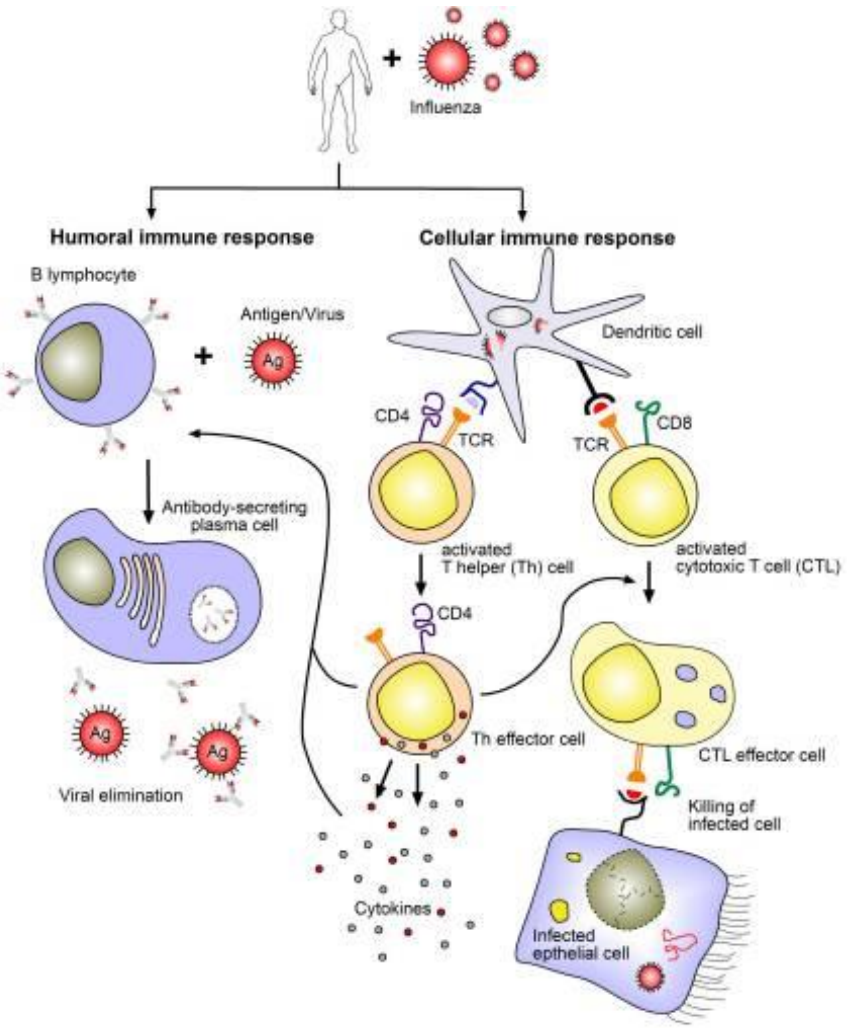
You have the option of remaining on HD or taking an ECD kidney…..which one would you pick?

A. HD
B. ECD kidney
C. Either

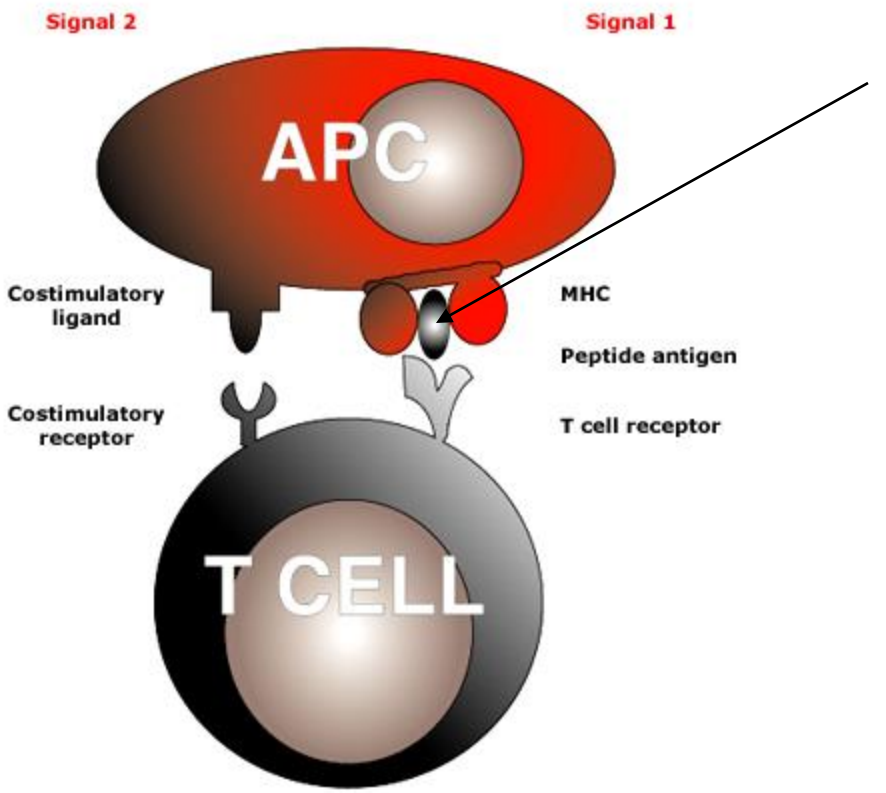


Adapted with permission from Ojo AO, Hanson JA, Meier-Kriesche H, et al. Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. *J Am Soc Nephrol.* 2001;12:589-597.

Transplant Immunology for non-transplant nephrologists

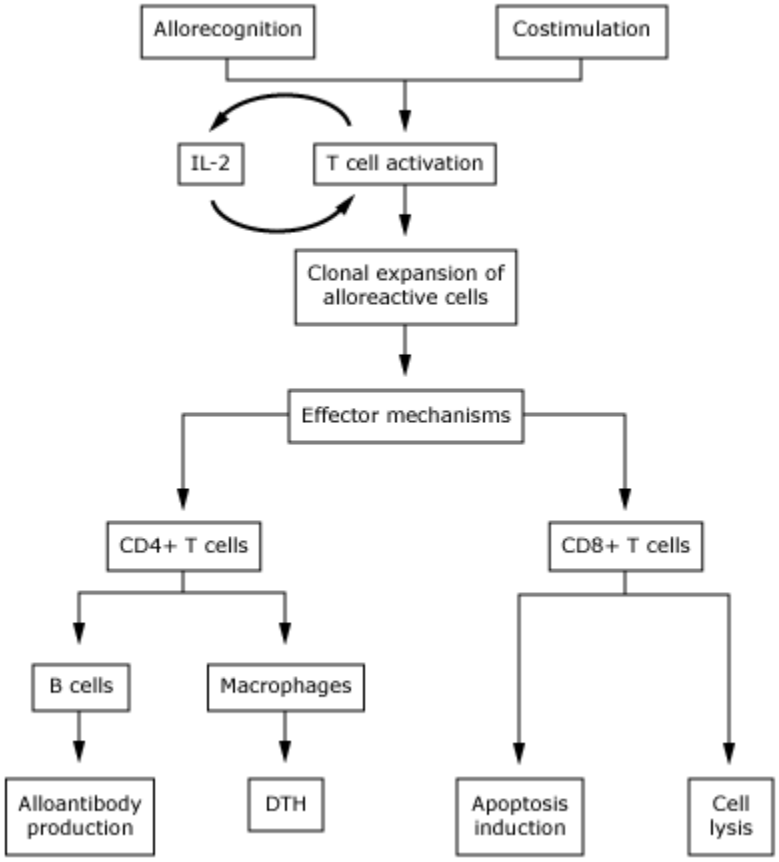

Influenza
Humoral immune response
Cellular immune response
B lymphocyte
Antigen/Virus
Ag
Dendritic cell
CD4
TCR
TCR
CD8
Antibody-secreting plasma cell
activated T helper (Th) cell
activated cytotoxic T cell (CTL)
CD4
Th effector cell
CTL effector cell
Killing of infected cell
Ag
Ag
Viral elimination
Cytokines
Infected epthelial cell

STEP 1 = Ag + APC meets T cell



antigen

STEP 2 = T cell activation



STEP 3 = Acute Rejection

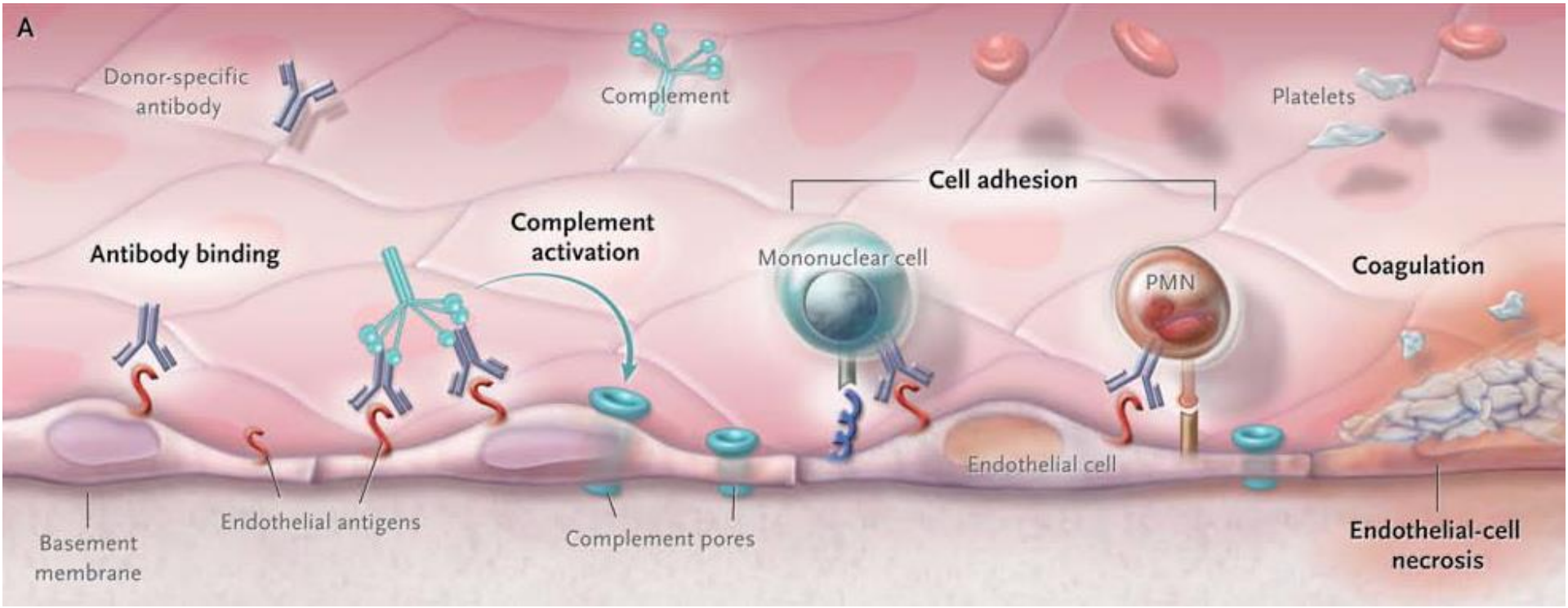
1. Acute Humoral rejection: B
2. Acute Cellular rejection: T

Question 8.

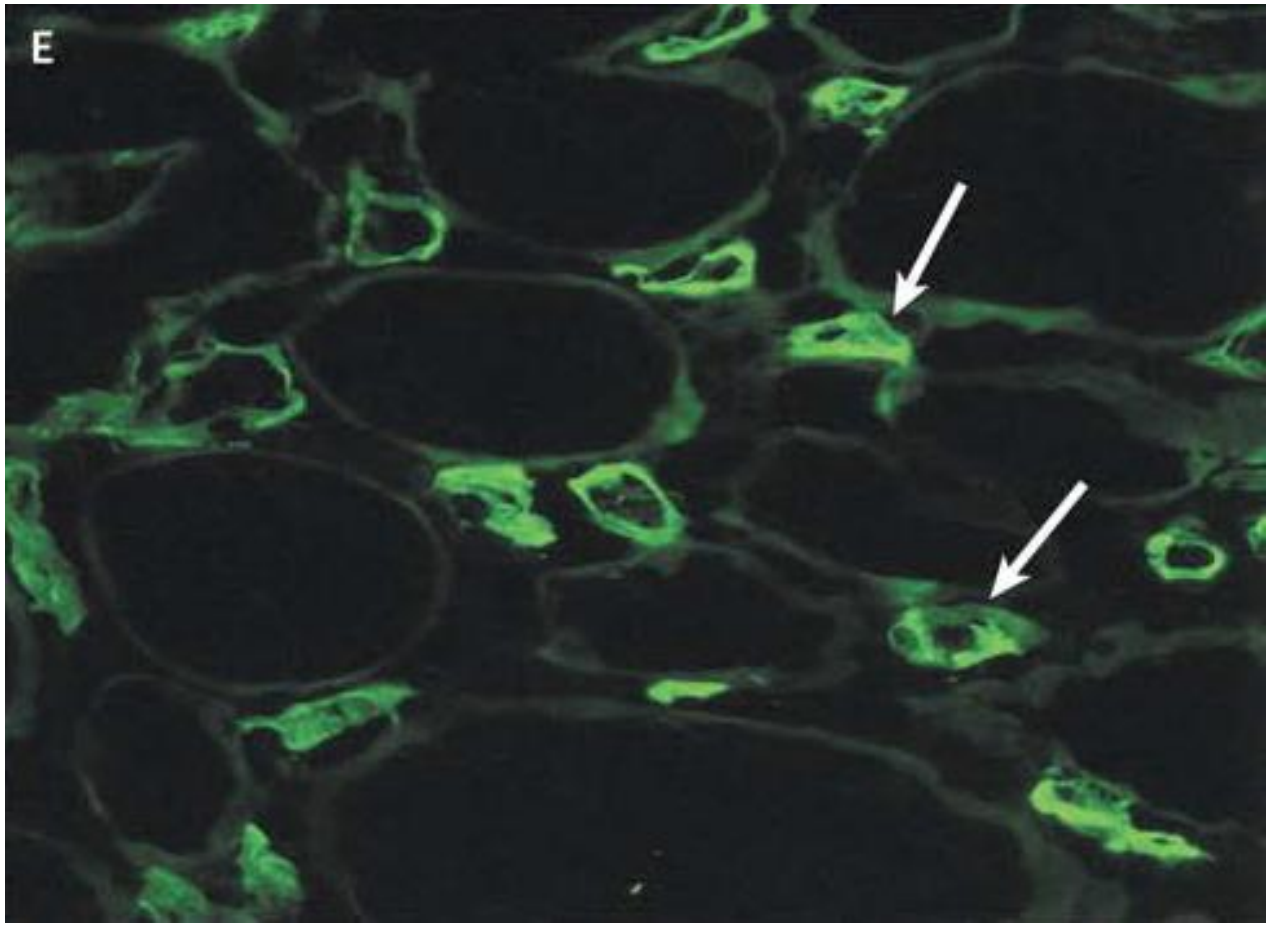
How can you diagnose acute rejection?

A. Rising Cr
B. Pain over transplant site
C. Elevated donor specific antibodies
D. Biopsy

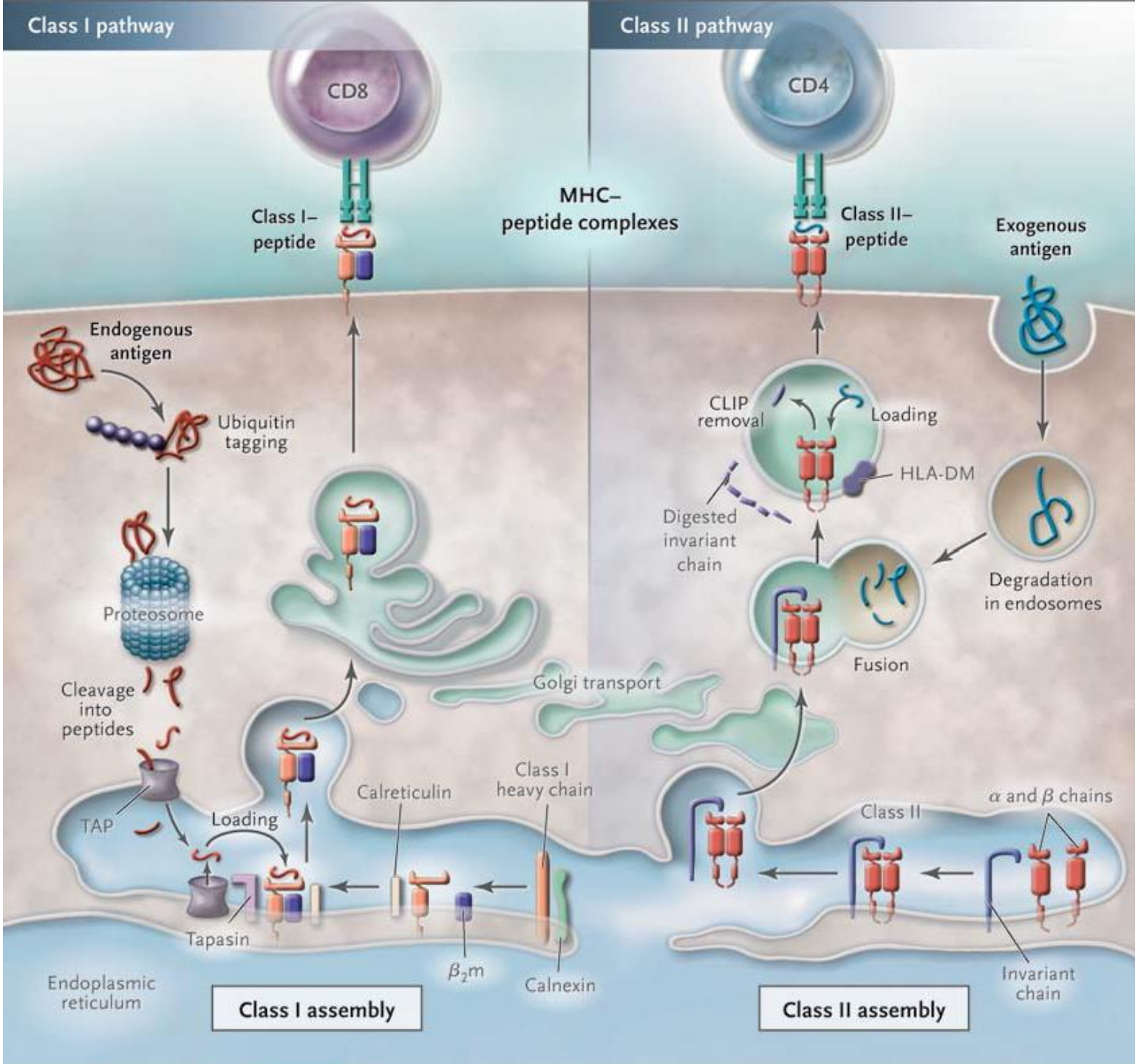
STEP 3 = Acute Humoral rejection: B

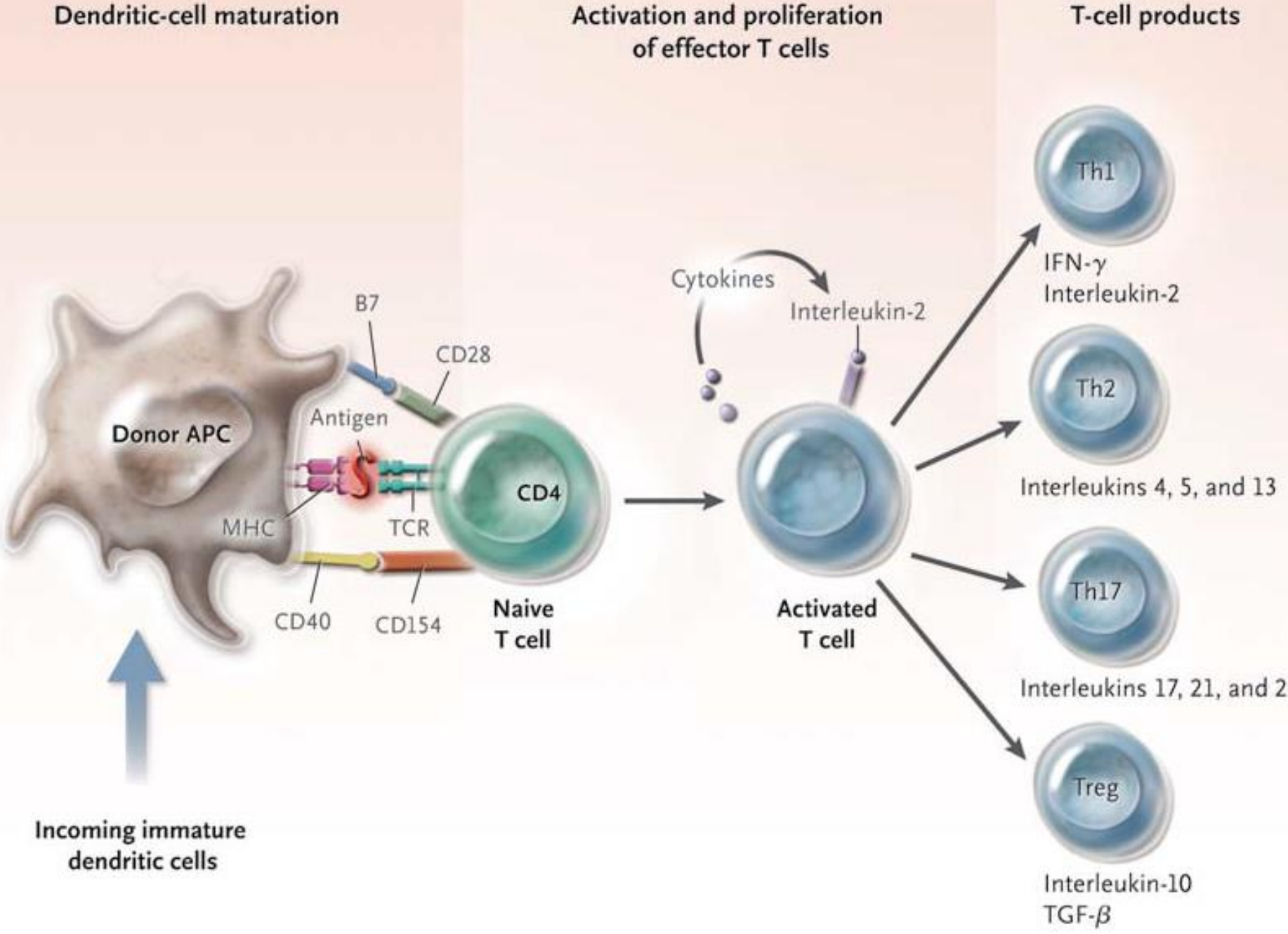


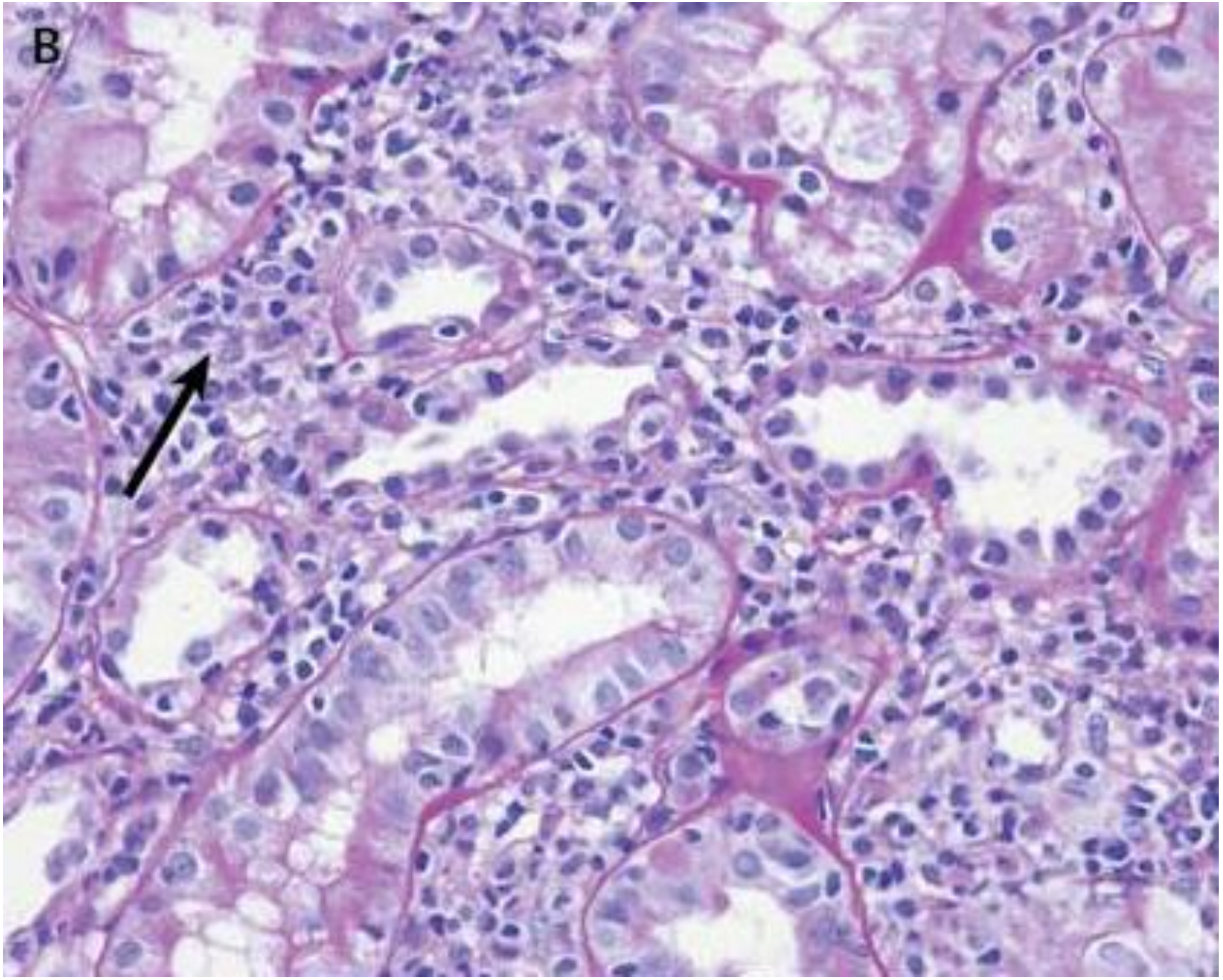
STEP 3 = Acute Humoral rejection: B

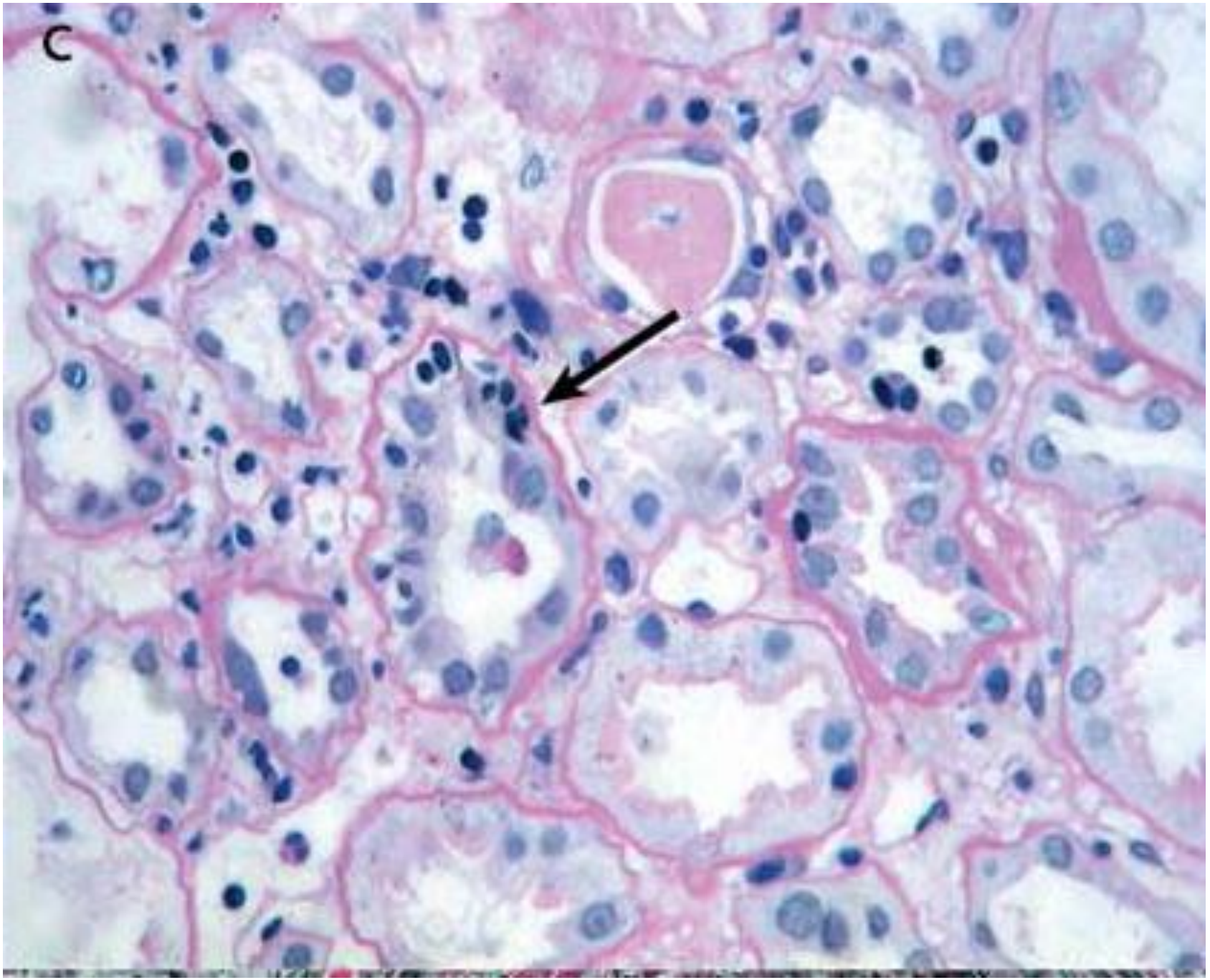


STEP 3 = Acute cellular rejection: T


Class I pathway
Class II pathway
CD8
CD4
MHC–
peptide complexes
Class I–
peptide
Class II–
peptide
Exogenous
antigen
Endogenous
antigen
Ubiquitin
tagging
CLIP
removal
Loading
HLA-DM
Digested
invariant
chain
Degradation
in endosomes
Proteosome
Fusion
Golgi transport
Cleavage
into
peptides
TAP
Loading
Calreticulin
Class I
heavy chain
Class II
α and β chains
Tapasin
β2m
Calnexin
Invariant
chain
Endoplasmic
reticulum
Class I assembly
Class II assembly


Dendritic-cell maturation
Activation and proliferation of effector T cells
T-cell products
Donor APC
B7
CD28
Antigen
MHC
TCR
CD4
CD40
CD154
Naive T cell
Incoming immature dendritic cells
Cytokines
Interleukin-2
Activated T cell
Th1
IFN-γ
Interleukin-2
Th2
Interleukins 4, 5, and 13
Th17
Interleukins 17, 21, and 2
Treg
Interleukin-10
TGF-β


B

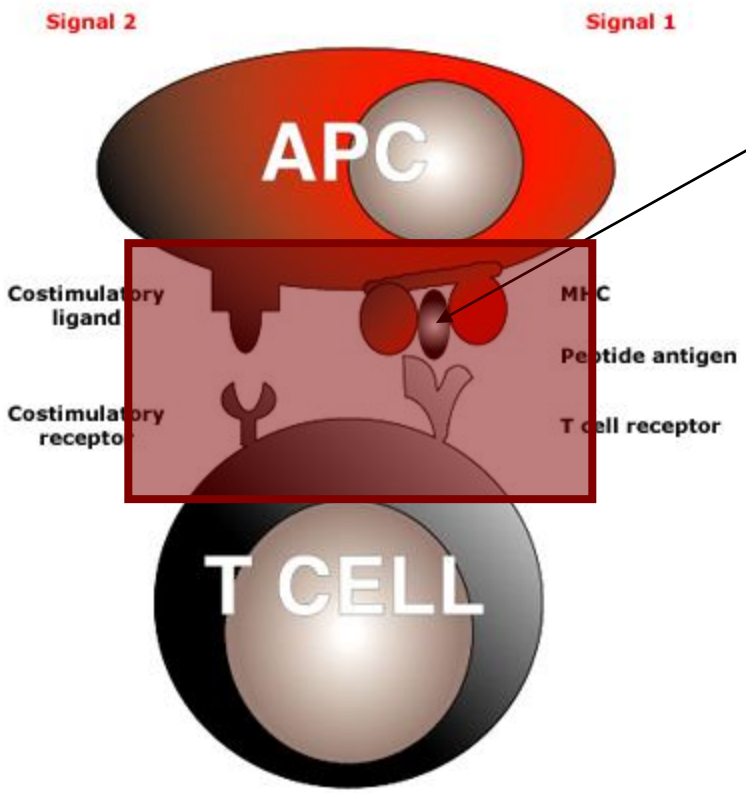

C

STEP 3 = Acute cellular rejection: T

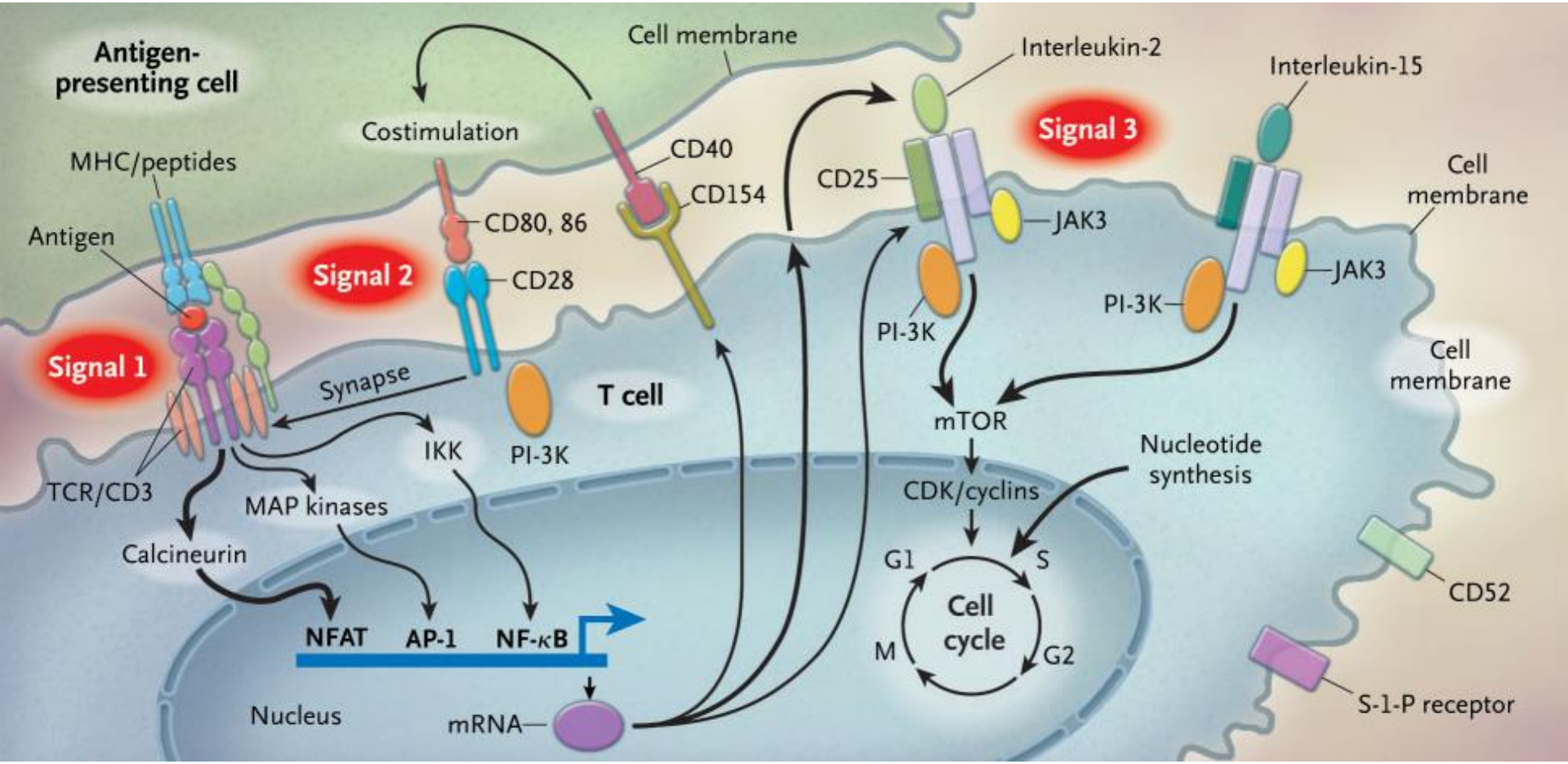
Table 1. Acute T-Cell–Mediated Rejection.*

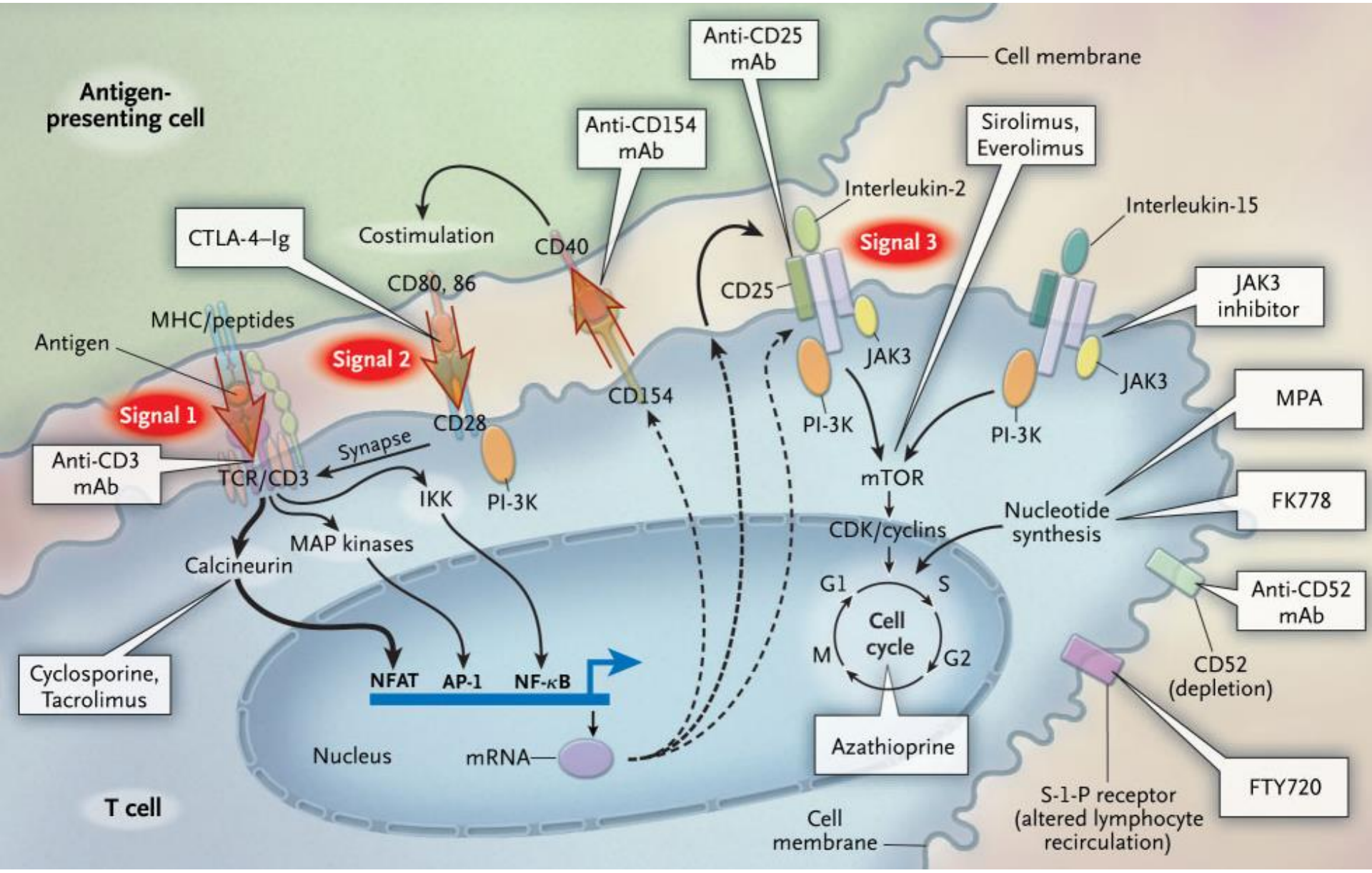
Banff Grade	Description
IA	Interstitial infiltration, with >25% of parenchyma affected (mononuclear-cell–infiltration inflammation score, 2 or 3) and foci of tubulitis (tubulitis score, 2)
IB	Interstitial infiltration; same as grade IA for infiltration but with foci of severe tubulitis (tubulitis score, 3)
IIA	Mild-to-moderate intimal arteritis (vasculitis score, 1)
IIB	Severe intimal arteritis comprising >25% of the luminal area (vasculitis score, 2)
III	Transmural arteritis or arterial fibrinoid change and necrosis of medial smooth-muscle cells with accompanying lymphocytic inflammation (vasculitis score, 3)

STEP 1 = Ag + APC meets T cell



antigen


Antigen-presenting cell
Cell membrane
Costimulation
MHC/peptides
CD40
CD154
CD80, 86
CD28
Antigen
Signal 2
Signal 1
Synapse
T cell
IKK
PI-3K
TCR/CD3
MAP kinases
Calcineurin
NFAT
AP-1
NF-κB
Nucleus
mRNA
Interleukin-2
Signal 3
CD25
JAK3
PI-3K
Interleukin-15
Cell membrane
JAK3
PI-3K
Cell membrane
mTOR
Nucleotide synthesis
CDK/cyclins
G1
S
Cell cycle
M
G2
CD52
S-1-P receptor


Antigen-presenting cell
Anti-CD25 mAb
Cell membrane
Anti-CD154 mAb
Sirolimus, Everolimus
Interleukin-2
Interleukin-15
CTLA-4–Ig
Costimulation
CD40
Signal 3
CD80, 86
CD25
JAK3 inhibitor
MHC/peptides
Antigen
Signal 2
JAK3
JAK3
CD154
MPA
Signal 1
CD28
PI-3K
PI-3K
Anti-CD3 mAb
Synapse
TCR/CD3
IKK
PI-3K
mTOR
FK778
Nucleotide synthesis
MAP kinases
CDK/cyclins
Calcineurin
G1
S
Cell cycle
M
G2
Anti-CD52 mAb
Cyclosporine, Tacrolimus
NFAT
AP-1
NF-κB
CD52 (depletion)
Azathioprine
Nucleus
mRNA
FTY720
T cell
S-1-P receptor (altered lymphocyte recirculation)
Cell membrane

	Induction (I)				I/M		Maintenance (M)				
	Basiliximab (Simulect)	Alemtuzumab (Campath)	Rituximab	Anti-Thymocyte Globulin (ATG)	Belatacept	Glucocorticoid	Tacrolimus (Prograf, Envarsus, Astagraf)	Cyclosporine (Neoral, Gengraf, Sandimmune)	Mycophenolic Acid (Cellcept, Myfortic)	Azathioprine	mTORi
Class	Chimeric murine mAb	Humanized mAB	mAB	Polyclonal igG (from rabbit/horse)	CTLA4-Ig	Steroids	Calcineurin inhibitor (CNI)	Calcineurin Inhibitor	Anti-metabolite (AM)	AM	mTORi
How It Works	IL-2 receptor antagonist .	Anti-CD52	Anti-CD20, B-cell depleting	Anti-thymocyte, T-cell depleting	Binds CD80/86 receptor on APC and blocks interaction with CD28 (co-stim)	Inhibits cytokine production	Binds FKBP, inhibits nuclear translocation of nuclear factor of activated T-cells (NFAT)	Binds cyclophilin and inhibits nuclear translocation of NFAT	Reversible inhibitor of IMPDH and blocks de novo purine synthesis	Disrupts salvage and de-novo purine synthesis .	Arrests cell cycle in G1-S phase
Timing	Non T-Cell depleting lasts 4-6 weeks	T cell depleting with 50% recovery at 3 yrs. B-cell recovery by 1 yr	lasts 12 mo (also used for AMR, DS)	lasts 3-6 months	I: dosed 10 mg/kg POD 0,4 week 2,4,8,12 M: 5 mg/kg monthly	I: Dosed with IV methylpred M: PO prednisone 5 mg daily	t ½ 9-18 hr, trough check 10-12 hours	t ½ Neoral/Gengraf: 5-18 hr t ½ 10-27 hours	t ½ Cellcept: 18 hr Myfortic: 15 hr Troughs not useful	t ½ 5 hr TPMT involved in metabolism	t ½ Sirolimus 62 hr Everolimus 30 hr
The Bad	Rare infusion reactions	Cytokine release syndrome (CRS); cytopenias	Infusion reactions	CRS, serum sickness, PTLD	PML; PTLD (recipient must be EBV IgG+); cytopenias	HTN; Bone dz;, HLD; Cushings; Weight gain	Alopecia; tremors; neurotoxicity. acute and chronic nephrotox	HTN; HLD; DM; Hyperkalemia; Gingival hyperplasia; Hirsutism; Acute and chronic nephrotoxicity	Contraindicated in pregnancy; GI upset, cytopenias	Hepatotoxic cytopenias (safe in pregnancy however)	Proteinuria Oral ulcers; ILD; cytopenias. Need 4 hours between Siro and CsA

mTOR: mammalian target of rapamycin inhibitor
PML: Progressive multifocal leukoencephalopathy
AMR: antibody mediated rejection
APC: antigen presenting cell
FKBP: FK binding protein
PTLD: post-transplant lymphoproliferative disorder

mAB: monoclonal antibody
IMDPH: inosine monophosphate dehydrogenase
TPMT: thiopurine methyltransferase
ILD: interstitial lung disease
IgG: Immunoglobulin G

DS: desensitization
CTLA4-Ig: cytotoxic t-lymphocyte associated protein 4 immunoglobulin

Maintenance

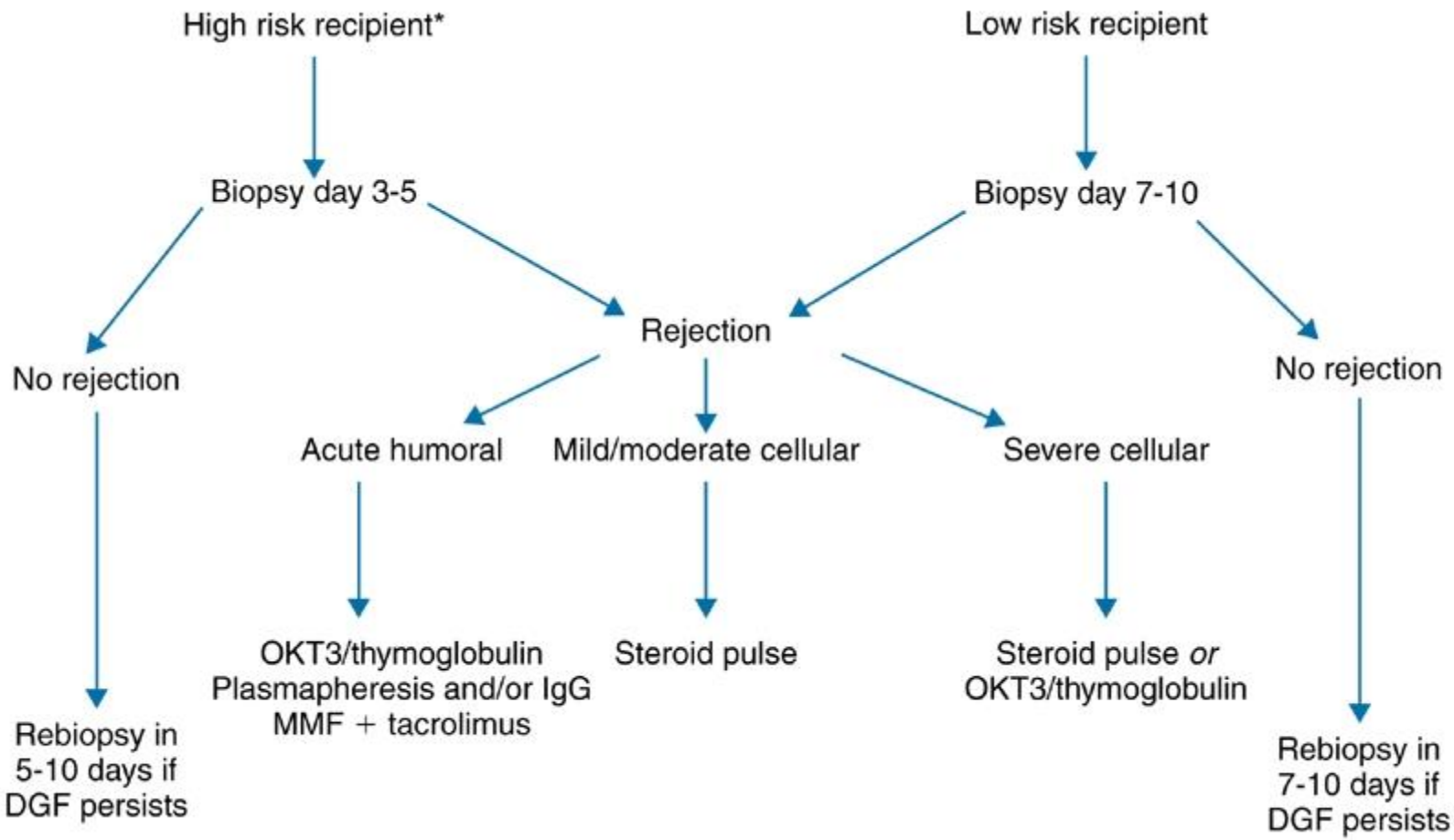
- Cellcept 1g BID
- Prograf
- Steroid free

Question 9.

How do you treat ACR Banff IIa?

Pick all options that apply

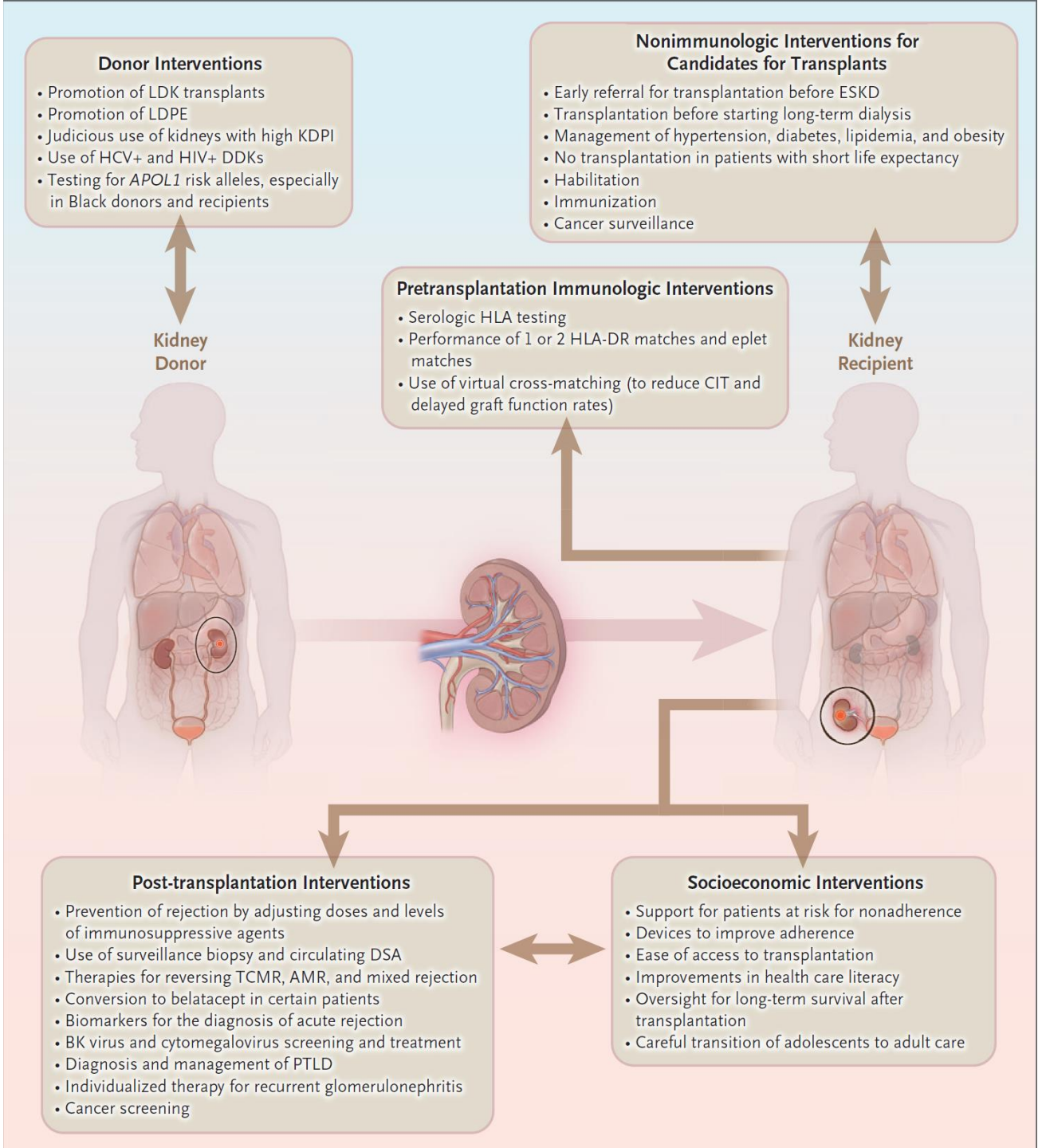
A. FK
B. MMF
C. Steroids
D. Thymoglobulin
E. Plasmapheresis
F. IVIG

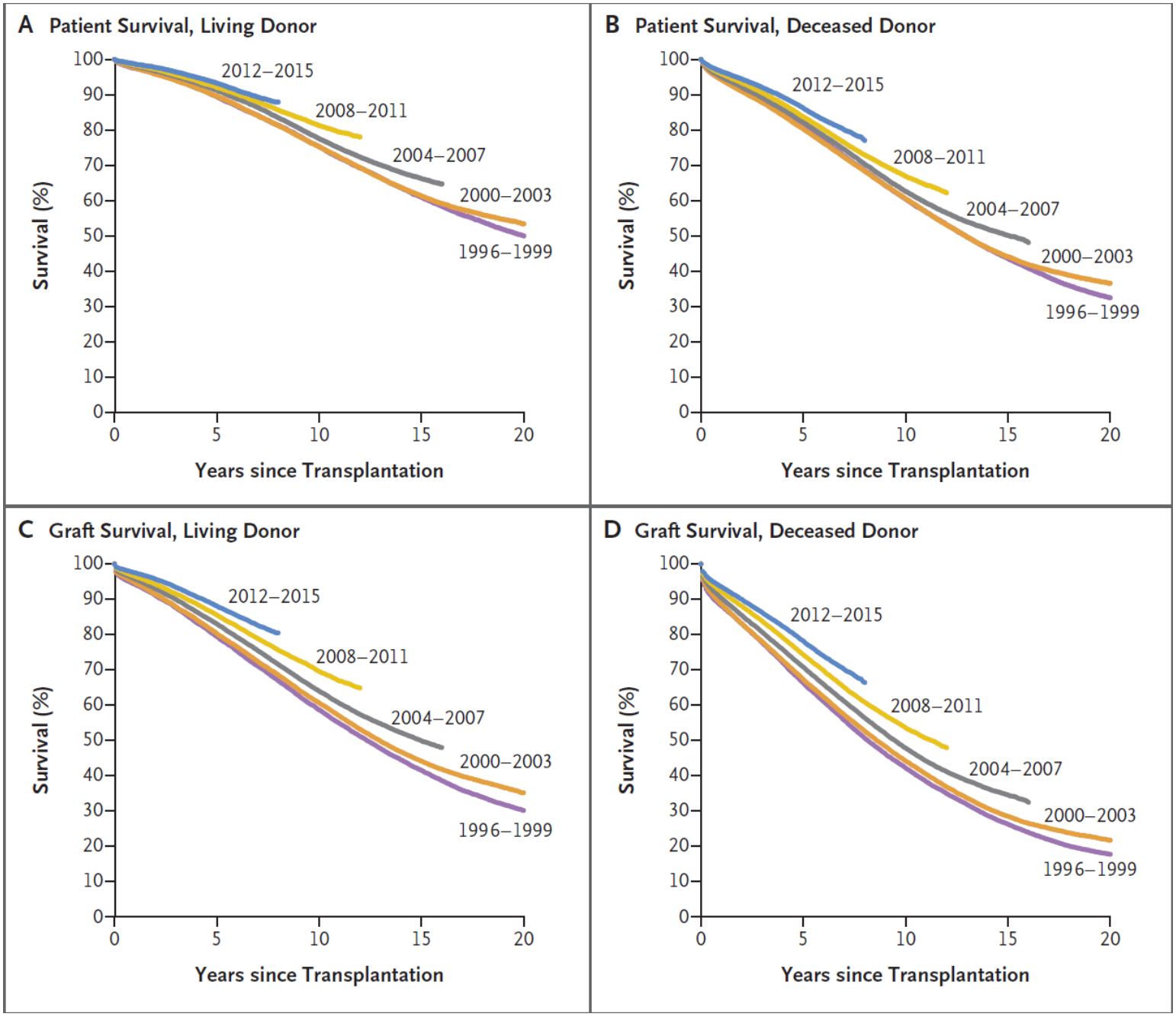


Question 10.

After 10 years of a living kidney transplant, what percentage of the transplants are still functioning?

A. 20.3
B. 3.8
C. 58.1
D. 77.8
E. 98.8


Donor Interventions
• Promotion of LDK transplants
• Promotion of LDPE
• Judicious use of kidneys with high KDPI
• Use of HCV+ and HIV+ DDKs
• Testing for APOL1 risk alleles, especially in Black donors and recipients
Nonimmunologic Interventions for Candidates for Transplants
• Early referral for transplantation before ESKD
• Transplantation before starting long-term dialysis
• Management of hypertension, diabetes, lipidemia, and obesity
• No transplantation in patients with short life expectancy
• Habilitation
• Immunization
• Cancer surveillance
Pretransplantation Immunologic Interventions
• Serologic HLA testing
• Performance of 1 or 2 HLA-DR matches and eplet matches
• Use of virtual cross-matching (to reduce CIT and delayed graft function rates)
Kidney Donor
Kidney Recipient
Post-transplantation Interventions
• Prevention of rejection by adjusting doses and levels of immunosuppressive agents
• Use of surveillance biopsy and circulating DSA
• Therapies for reversing TCMR, AMR, and mixed rejection
• Conversion to belatacept in certain patients
• Biomarkers for the diagnosis of acute rejection
• BK virus and cytomegalovirus screening and treatment
• Diagnosis and management of PTLD
• Individualized therapy for recurrent glomerulonephritis
• Cancer screening
Socioeconomic Interventions
• Support for patients at risk for nonadherence
• Devices to improve adherence
• Ease of access to transplantation
• Improvements in health care literacy
• Oversight for long-term survival after transplantation
• Careful transition of adolescents to adult care


A Patient Survival, Living Donor
B Patient Survival, Deceased Donor
C Graft Survival, Living Donor
D Graft Survival, Deceased Donor
Survival (%)
Years since Transplantation
2012–2015
2008–2011
2004–2007
2000–2003
1996–1999
0
10
20
30
40
50
60
70
80
90
100
0
5
10
15
20

Questions?