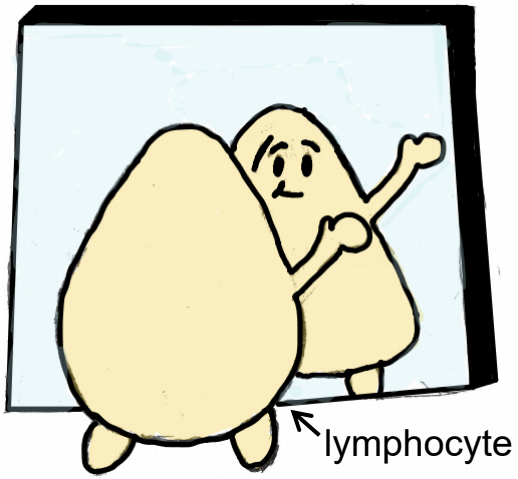
MAYO CLINIC

Graft vs Host Disease (GVHD): The Enemy within Me



Stephanie Gore, PharmD, MPH
PGY2 Solid Organ Transplant Resident

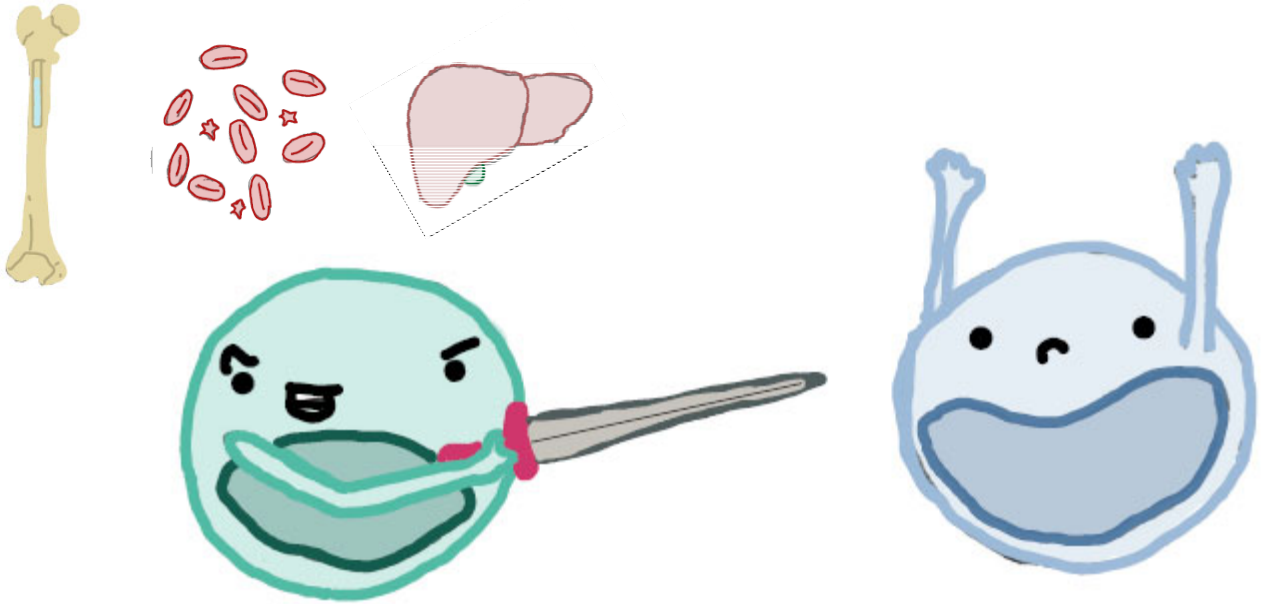
Objectives

- Explain the pathophysiology of Graft vs. Host Disease (GVHD) in Solid Organ Transplant (SOT)
- Recognize current therapeutic options for managing GVHD in SOT
- Discuss the available evidence and outline recommendations for the management of GVHD in SOT

Graft-Versus-Host-Disease

Section of transplanted or donated tissue

Tissues of the person receiving the transplant

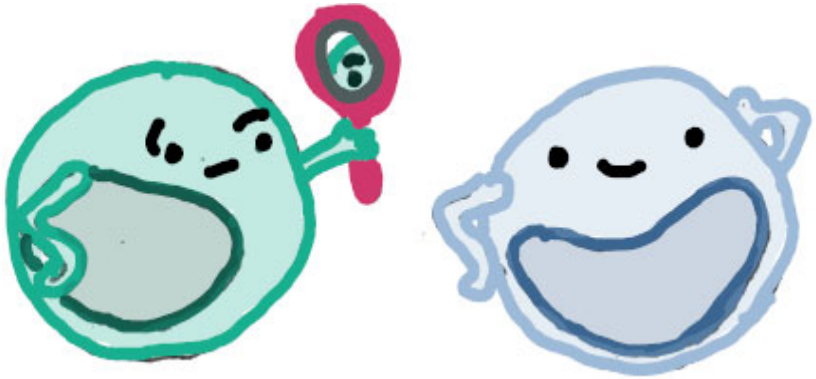


Donor cell

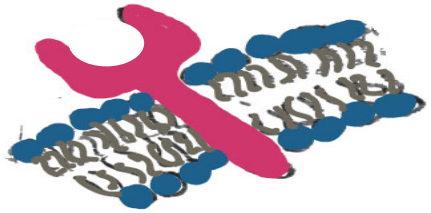
Recipient cell

Immune System

- Fight against anything:
  - Foreign that might cause harm without harming the body's own cells
- Cells trained to distinguish non-self/foreign from self



- Histocompatibility genes
- Major histocompatibility complex (MHC proteins)- also known as Human Leukocyte Antigens (HLA)



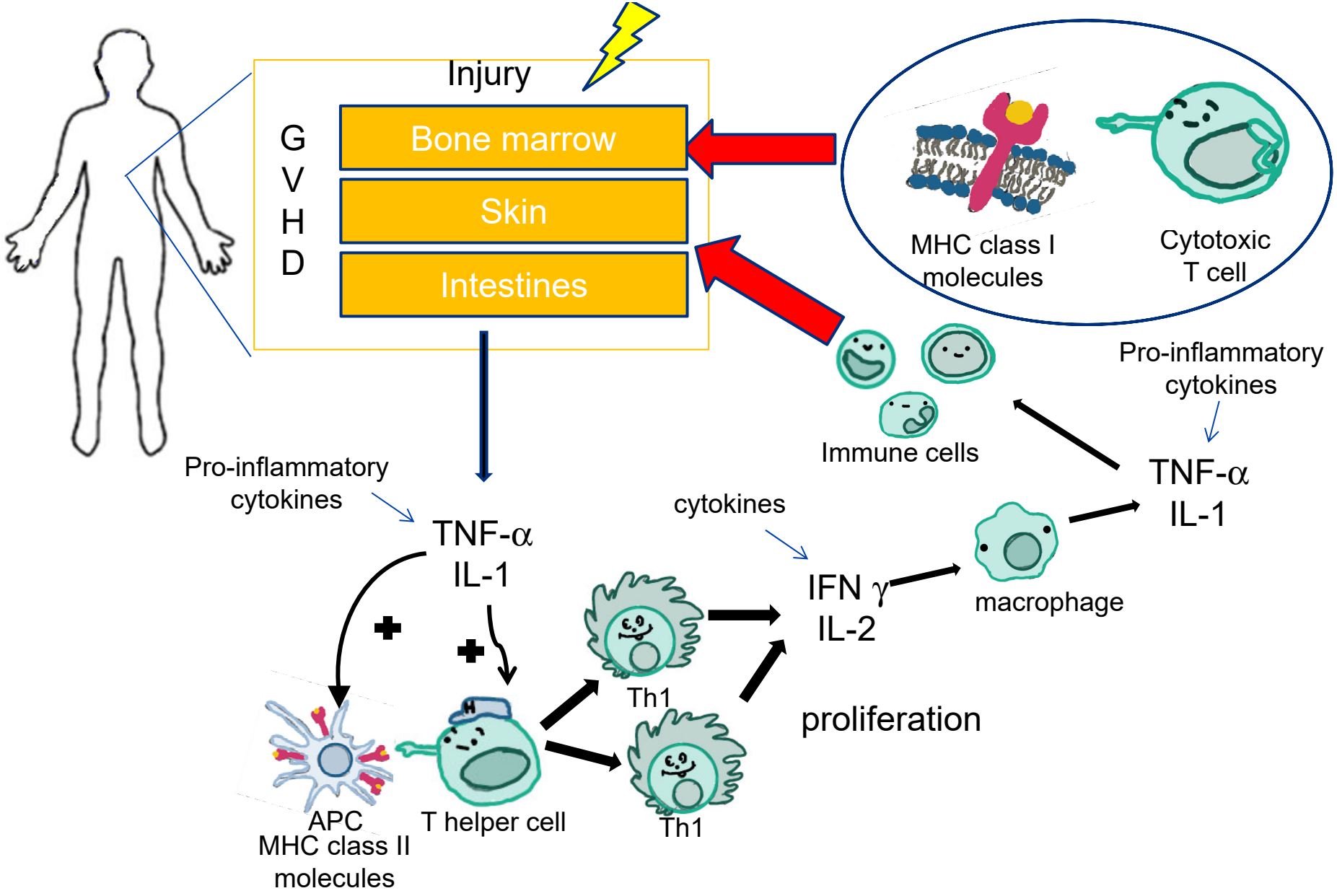
  - MHC Class I
    - Expressed on all nucleated cells
  - MHC Class II
    - Only expressed on Antigen Presenting Cells

Pathogenesis

Phase I

Graft must contain immune cells

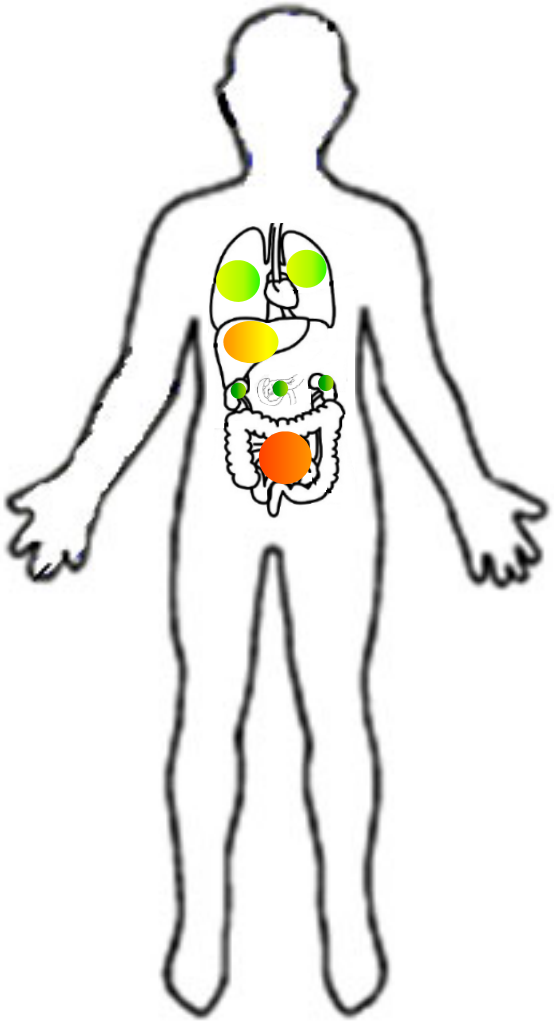
Am J Transplant. 2004; 4: 466–474



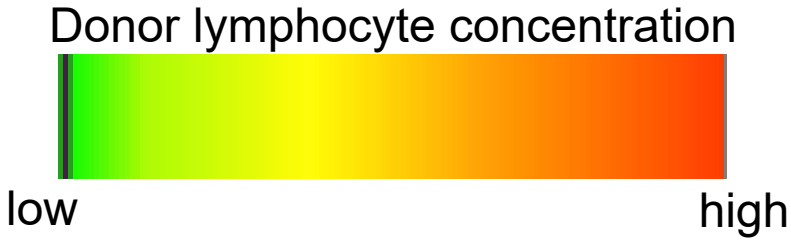
Am J Transplant. 2004; 4: 466–474

APC: antigen presenting cell
Th1: Type 1 helper T cells

Prevalence of GVHD in SOT



Organ	Prevalence
Small bowel	5.6%
Liver	0.1%-2%
Lung	0.04%
Kidney or pancreas	Extremely rare
Heart	Not reported



Am J Transplant. 2004; 4: 466–474
Crit Care Nurse. 2016; 36(3):e7-e11

Clinical Presentation

Am J Transplant. 2004; 4: 466–474

Risk Factors for GVHD

Factors	GVHD (n=8)	Controls (n=24)	P-value
Age difference (D-R, yr)	29	10	0.03
D younger than R >20 yr (%)	88	33	0.01
Any HLA match (%)	63	58	1
Any HLA class I match (%)	63	25	0.09
Any HLA class II match (%)	25	42	0.7

P< 0.01

Factors	Relative risk (95% CI)	P-value
Age difference (D-R)	1.06 (1.01-1.12) per yr	0.02
Any HLA class I match	9.76 (1.14-83.64)	0.04

MAYO CLINIC

Clin Transplant. 2015; 29:1063-1066

Meet AB: Donor/Recipient Information

AB underwent liver transplant with basiliximab induction

Initial immunosuppression:
- **Tacrolimus**
- **Mycophenolate mofetil**
- **Steroid taper**

- Recipient: 69 year old male
- Donor: 28 year old male
- ABO (D/R): O Pos/O Pos
- HLA matching: HLA class I: 5 of 6 mismatch
- CMV D-/R+; EBV D+/R+

HLA: human leukocyte antigen
DSA: Donor specific antibody
CMV: Cytomegalovirus
EBV: Epstein-Barr virus

What risk factors for GVHD does AB have?

- A) Age difference between D and R > 20 years
- B) CMV status
- C) HLA class I match
- D) Both A and C
- E) All of the above

DSA: Donor specific antibody
CMV: Cytomegalovirus

R: Recipient
D: Donor
HLA: human leukocyte antigen

AB's Timeline of Events

Symptoms

Presents with ongoing diarrhea, rash, and CMV viremia

CMV: Cytomegalovirus

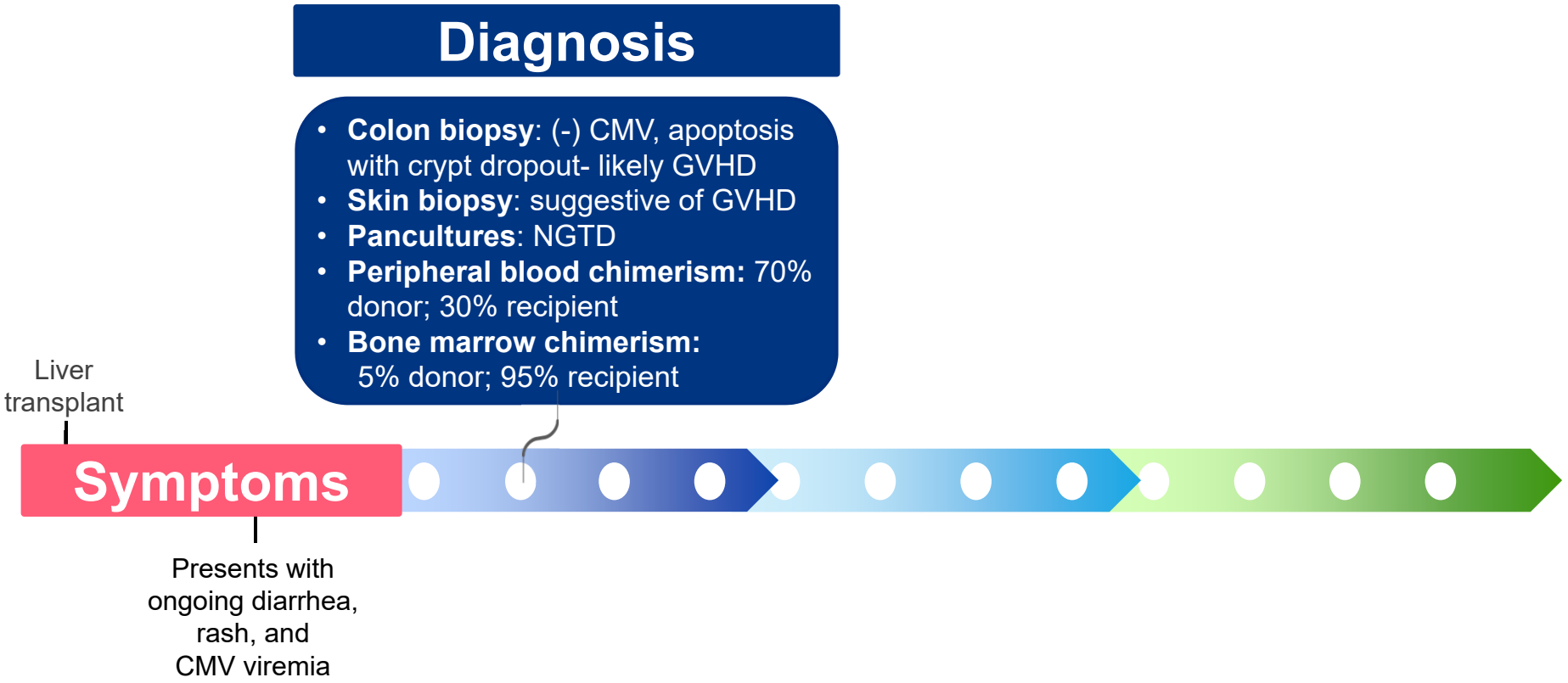
Proposed Diagnostics: Three Steps

Diagnostic workup	• Skin biopsy • Colonoscopy/flexible sigmoidoscopy • Bone marrow biopsy
Infectious workup	• Pancultures, including fungal cultures • Stool C. *difficile* • Serum CMV PCR
Confirmatory testing	• Chimerism studies • Donor lymphocyte macrochimerism > 1% in peripheral blood ± bone marrow

Transplantation. 2016; 100(12): 2661–2670

CMV: Cytomegalovirus

AB's Timeline of Events



CMV: Cytomegalovirus
GVHD: graft vs host disease
NGTD: no growth to date

Treatment Options

Decrease/ Discontinue immunosuppression

Increase immunosuppression

Monoclonal antibody (e.g. IL2R,TNFα)

Extracorporeal photopheresis

HSCT

HSCT: hematopoietic stem cell transplant

Decrease/Discontinue Immunosuppression

Study	Age (yr) / sex	POD onset	Initial IS	Treatment	Outcome
Lehner, 2002	29/M	32	CsA, MMF	Discontinue	Survived
Walling, 2004	60/M	70	Tac, MMF, Pred	Decrease	Survived
Chinnakotla, 2006	58/M	70	Tac, MMF, Pred	Discontinue	Survived
	53/M	126	Tac, MMF, Pred	Decrease	Survived
	62/M	14	CsA, SRL, Pred	Decrease	Expired
Wang, 2007	59/M	31	CsA, Pred	Decrease	Survived

Transplant Proc. 2007;39:1696–8
J Cutan Pathol 2004: 31: 179–184
Transplantation. 2002;73:307–10
Liver Transpl 2006; 13(1): 157-161

IS: immunosuppression
Tac: tacrolimus
MMF: mycophenolate mofetil

Pred: prenisone
CsA: cyclosporine
SRL: sirolimus
POD: post-op day

Increase Immunosuppression

Design

- Comprehensive review of literature
- 80 articles with total of 156 cases identified between 1988 and 2014

Population

- 130 patients with GVHD after liver transplant with reported treatment regimens

Treatment

- Immunosuppression decreased in 6.2% of patients (n=8)
- Immunosuppression intensified in 93.8% of patients (n=122)

Transplantation. 2016; 100 (12) 2661-2670.

GVHD: Graft vs host disease

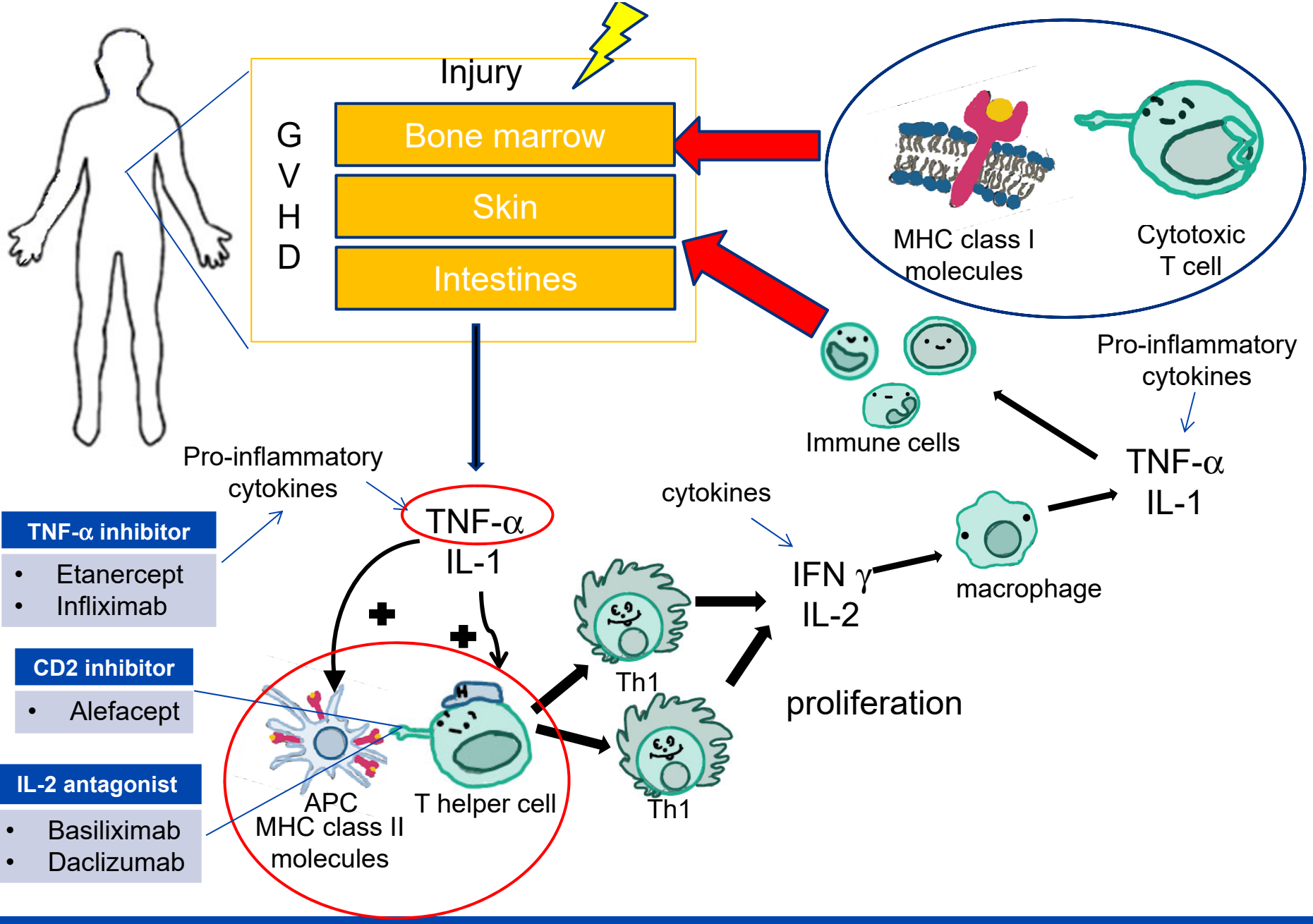
Increase Immunosuppression

Treatment regimen	Number of patients	Mortality %
Steroid containing regimens		
Steroids only	25	84
Steroids + CNI dose increase	8	75
ATG containing regimens		
ATG + steroids	22	81
ATG + steroids+ CNI	3	100
IL-2 antagonist containing regimens		
IL-2 antagonist +steroids	12	58
IL-2 antagonist +steroids + CNI	2	100
Other treatment regimens		
TNF- α inhibitors +steroids +ATG	4	25
Alefacept+ steroids+ ATG	7	28

MAYO CLINIC

Transplantation. 2016; 100 (12) 2661-2670.

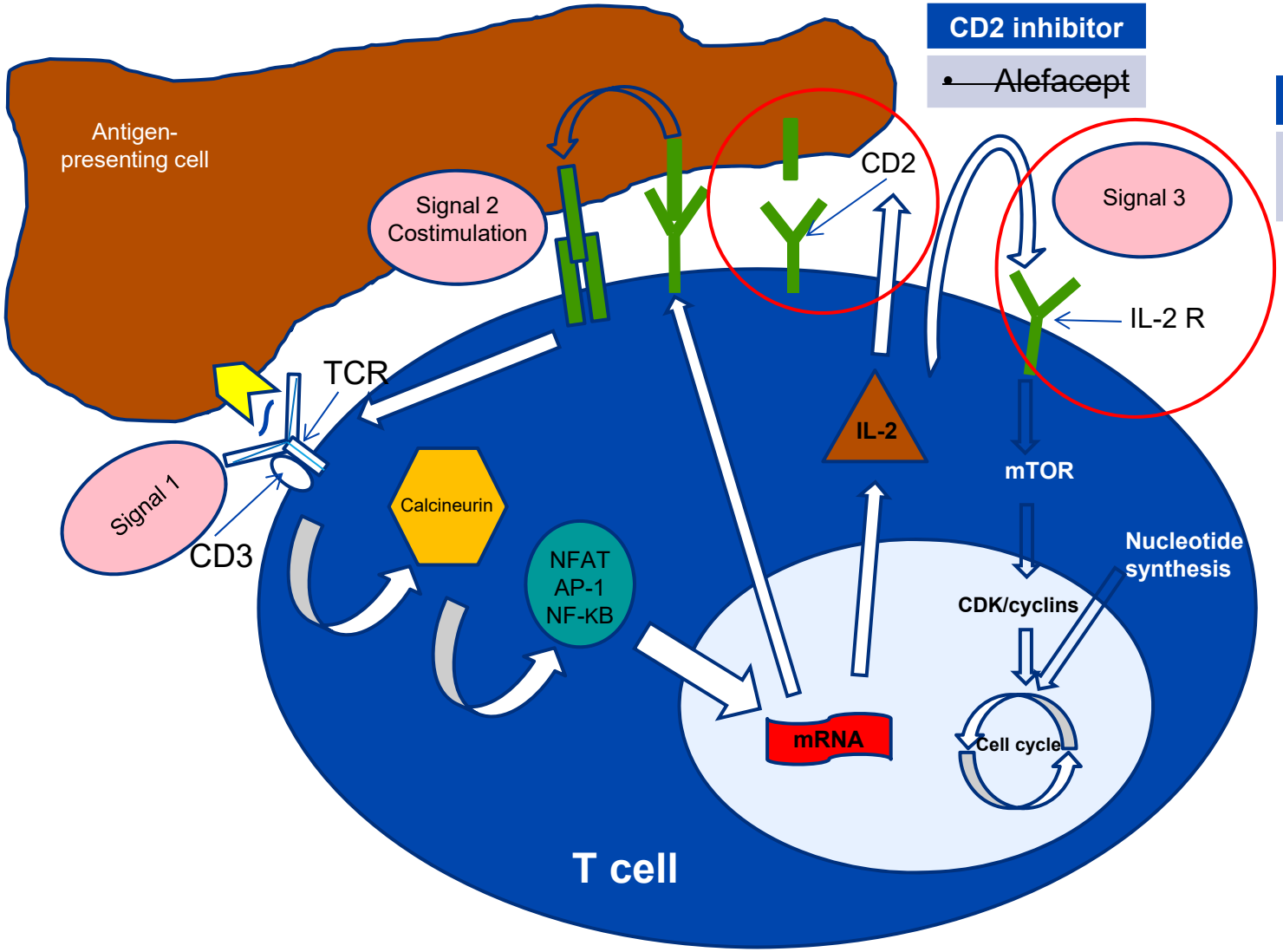
CNI: Calcineurin inhibitors
ATG: anti-thymocyte globulin



Am J Transplant. 2004; 4: 466–474

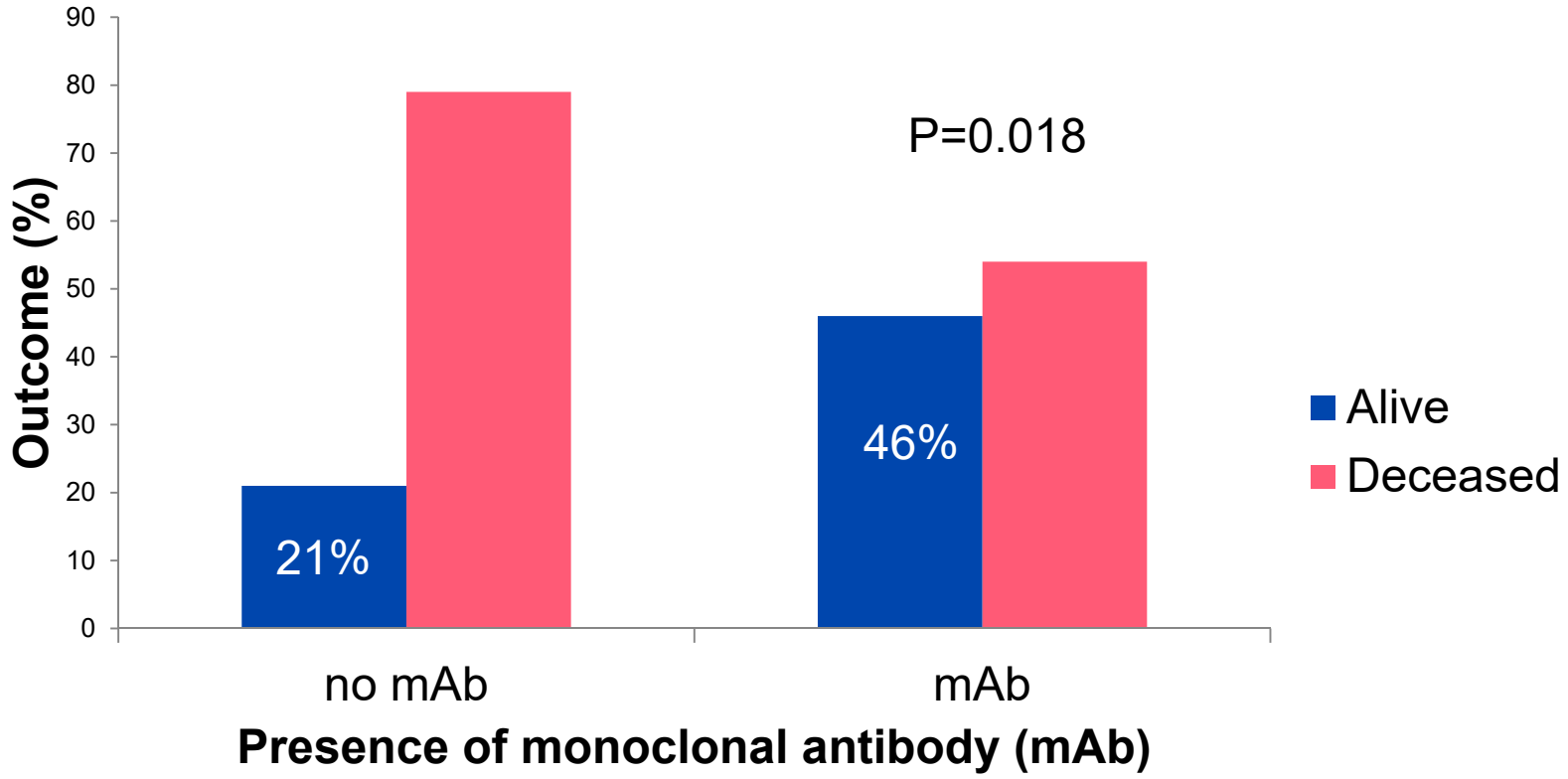
APC: antigen presenting cell
Th1: Type 1 helper T cells

Targets of Immunosuppression



N Engl J Med. 2004; 351 (26): 2715-2729

IL-2R and TNF-α



Conclusion: mAb has beneficial effect and there is a promising role for IL-2R/TNF-α in treatment of GVHD after liver transplant

Am J Transplant. 2018; 18: 3007-3020

mAb: monoclonal antibody
GVHD: graft vs host disease

Etanercept (TNF-α inhibitor)

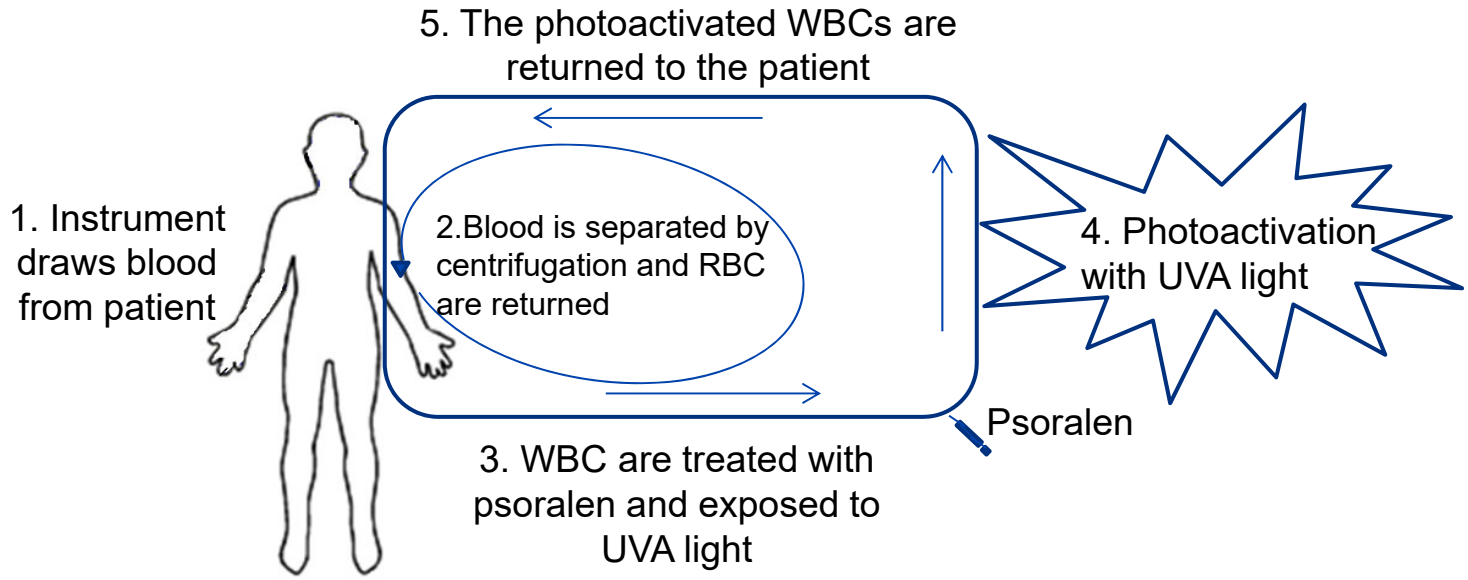
Age (yr) / sex	POD onset	Initial IS	Treatment				Outcome
65/M	20	Tac, Aza, Pred	IS discontinue **[POD22]**	IVMP **[POD28]**	IS restarted at lower doses **[POD28]**	Etanercept 25 mg SQ twice a week **[POD28]**	Survived **[POD42]** [invasive fungal infection]
61/M	9	ERL, Tac, Pred	Decrease IS **[POD9]**	IVMP, ATG **[POD19]**	IS restarted with lower doses **[POD19]**	Etanercept 50mg weekly **[POD19]**	Expired **[POD39]** [multiple infections]

Liver Transpl . 2009; 15:421-426
Exp Clin Transplant . 2018; doi: 10.6002/ect.2017.0231. [Epub ahead of print]

IS: immunosuppression
IVMP: intravenous methylprednisolone
ATG: anti-thymocyte globulin

Tac: tacrolimus
Aza: azathioprine
Pred: prednisone
ERL:everolimus

Extracorporeal Photopheresis



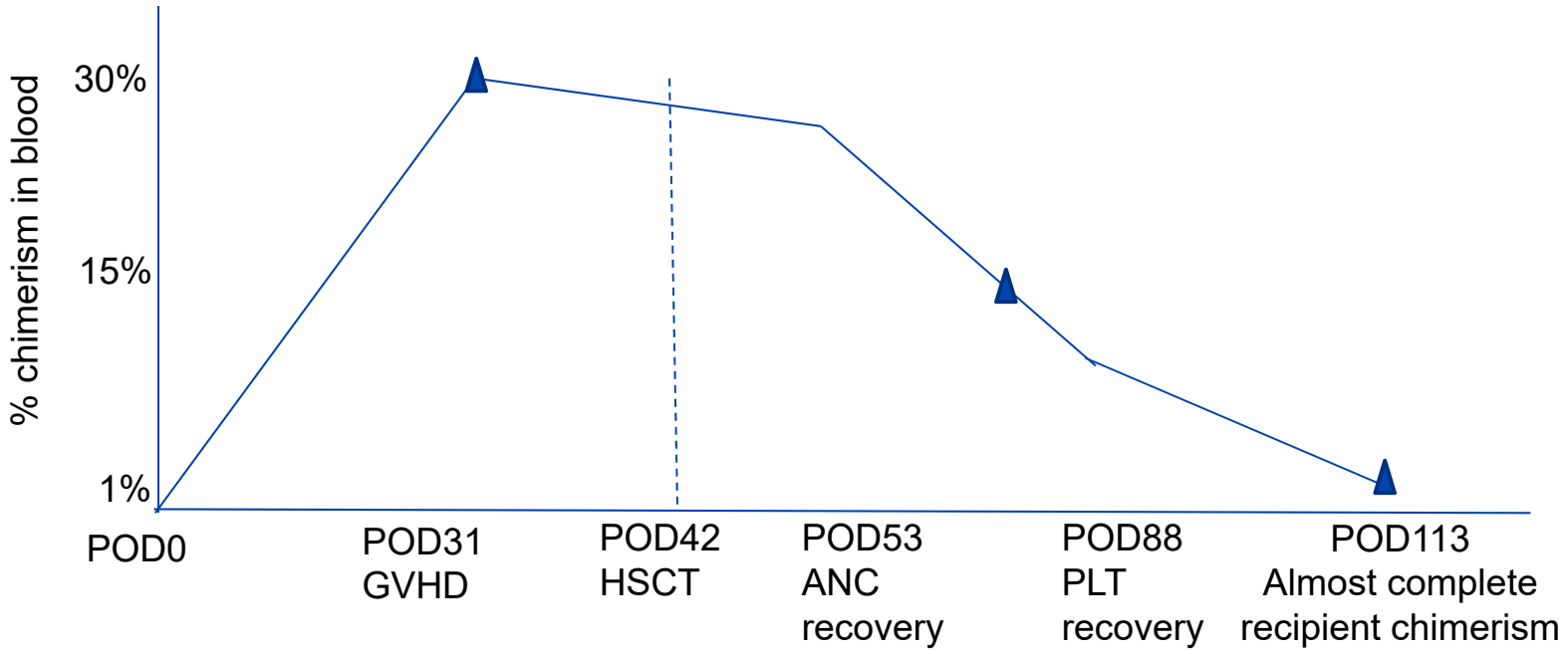
Age (yr) / sex	POD onset	Initial IS	Initial Treatment	Refractory treatment	Outcome
48/M	17	Basiliximab, Tac, MMF, Pred	IVMP, Decrease IS	32 sessions of ECP, with resolution of symptoms	Survived
52	22-68 days after OLT	ATG, Tac, MMF, Pred	IVMP, Decrease IS	Etanercept, ECP (sessions not defined)	ACR, GVHD resolved
67					Hospice

ACG Case Rep J 2017; 4: 48
Am J Transplant. 2017; 17 (suppl 3).

ECP: Extracorporeal photopheresis
IVMP: intravenous methylprednisolone
ATG: anti-thymocyte globulin
Tac: tacrolimus
Pred: prednisone
IS: immunosuppression
POD: post operative day
ACR: acute cellular rejection
MMF: mycophenolate mofetil
WBC: white blood cells
RBC: Red blood cells

Hematopoietic Stem Cell Transplant

Age(yr)/ sex	POD onset	Initial IS	Initial treatment	Refractory treatment	Outcome
74 yoF	28	Tac, Pred	IVMP, MMF, IVIG, ATG	HSCT with Tac, MMF, Pred	Survived



Blood (2011) 118 (12): 3448–3449.

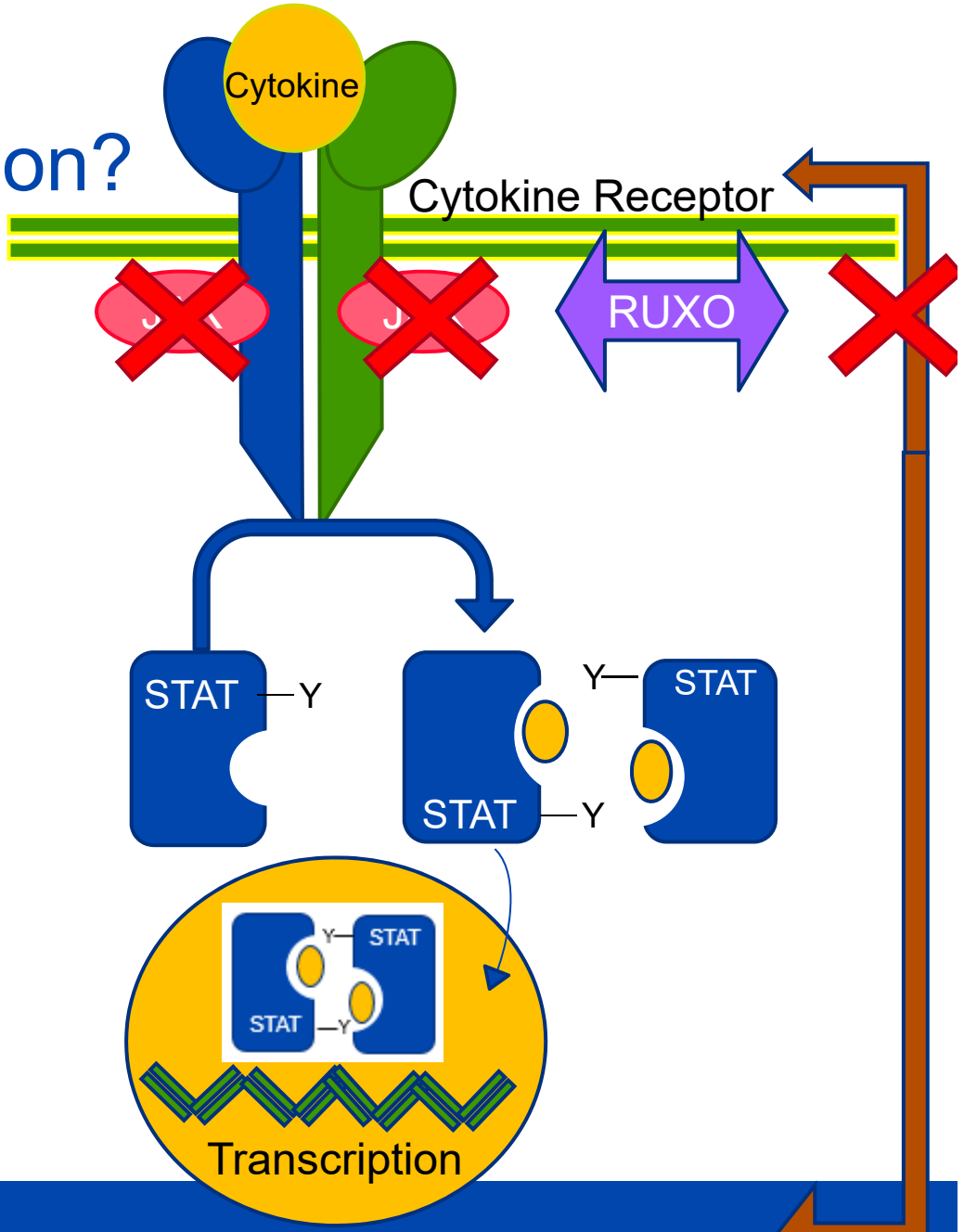
IVMP: intravenous methylprednisolone
ANC: absolute neutrophil count
Tac: tacrolimus
Pred: prenisone

HSCT: Hematopoietic stem cell transplant
IS: immunosuppression
POD: post operative day

PLT: platelet
MMF: mycophenolate mofetil
ATG:anti-thymoglobulin
IVIG: intravenous immunoglobulin

Ruxolitinib- A New Option?

- Ruxolitinib approved for steroid refractory acute GVHD in HSCT
- The JAK-STAT signaling pathway helps regulate several immune cell types important in the pathogenesis of GVHD
- Animal studies suggest a decreased in inflammatory cytokines in colon and reduces immune cell infiltration in the colon



Ruxo: ruxolitinib
HSCT: Hematopoietic stem cell transplant
GVHD: graft vs host disease

Ruxolitinib

Age (yr) / sex	POD onset	Initial IS	Treatment		Outcome
66/M	21	Basiliximab,Tac, MMF, Pred	Increase IS **[POD21]**	Ruxolitinib 5 mg twice daily **[POD35]**	Full recipient chimerism one month after treatment
63/M	28	Basiliximab, Tac, MMF, Pred	Decrease IS **[POD28]**	Ruxolitinib 5 mg twice daily	After 5 weeks of treatment, 6% donor chimerism. 1 month later, expired from infection

Am J Transplant.2019;00:1–4.

IS: immunosuppression
POD: post operative day

Tac: tacrolimus
MMF: mycophenolate mofetil
Pred: prednisone

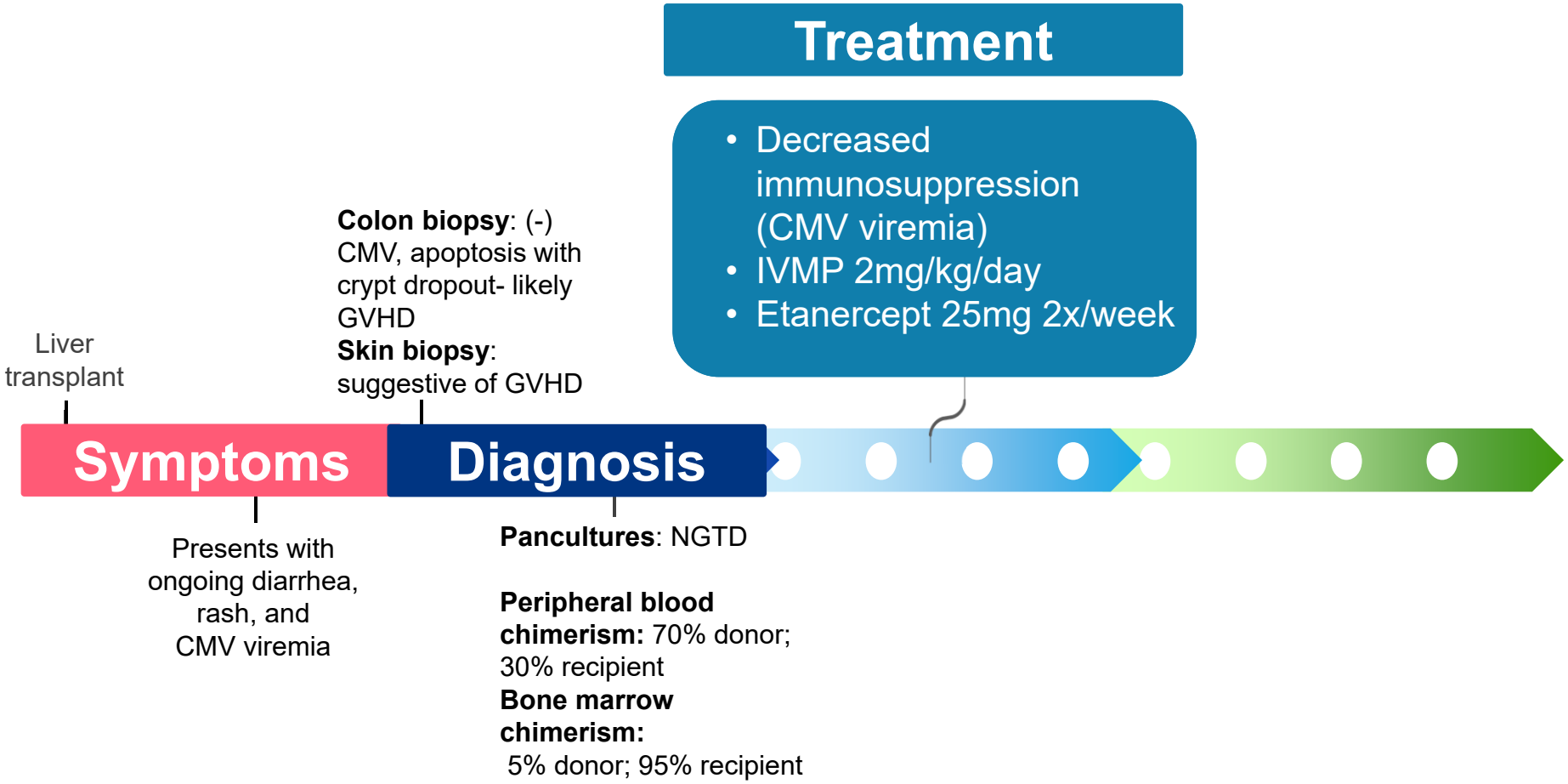
Proposed Treatment

First-line	• High dose methylprednisolone start at 2mg/kg/day
Second-line	• TNF-α (e.g. Etanercept)
Refractory	• Ruxolitinib • Extracorporeal photopheresis • HSCT

*Provide supportive care as needed and consider antimicrobial prophylaxis (based on patient specific factors)

Transplantation. 2016; 100(12): 2661–2670
HSCT: hematopoietic stem cell transplant

AB's Timeline of Events



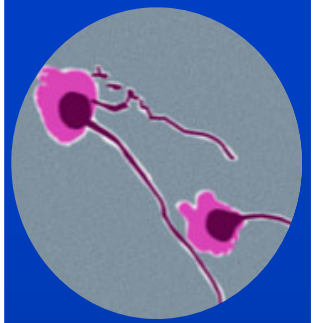
CMV: Cytomegalovirus
GVHD: graft vs host disease
NGTD: no growth to date
IVMP: intravenous methylprednisolone

What initial treatment is best to start when GVHD is suspected in a liver transplant patient?

- A) IVMP at 2 mg/kg/day
- B) Wait for confirmatory results before initiating therapy
- C) Stop all immunosuppression
- D) No therapy is necessary

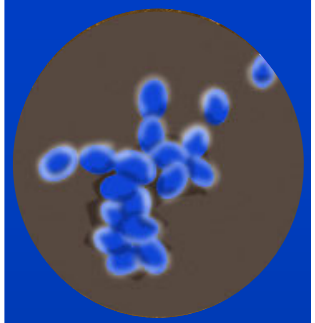
IVMP: intravenous methylprednisolone
GVHD: graft vs host disease

Infection Prophylaxis

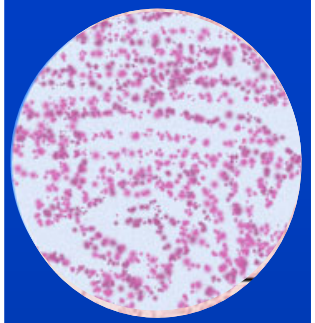


Invasive aspergillosis (36%)

Disseminated candidiasis (28%)



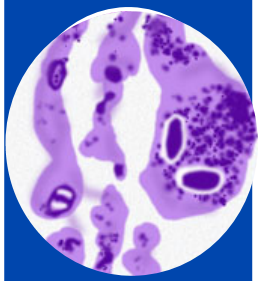
Enterococci (28%)



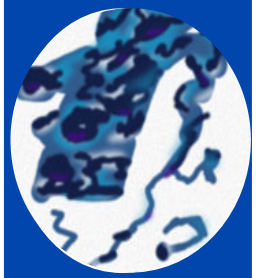
Enterobacter (2%)

Consider posaconazole/ voriconazole vs Echinocandin

Consider broad spectrum antibiotics* (Based on patient specific factors)



Cytomegalovirus



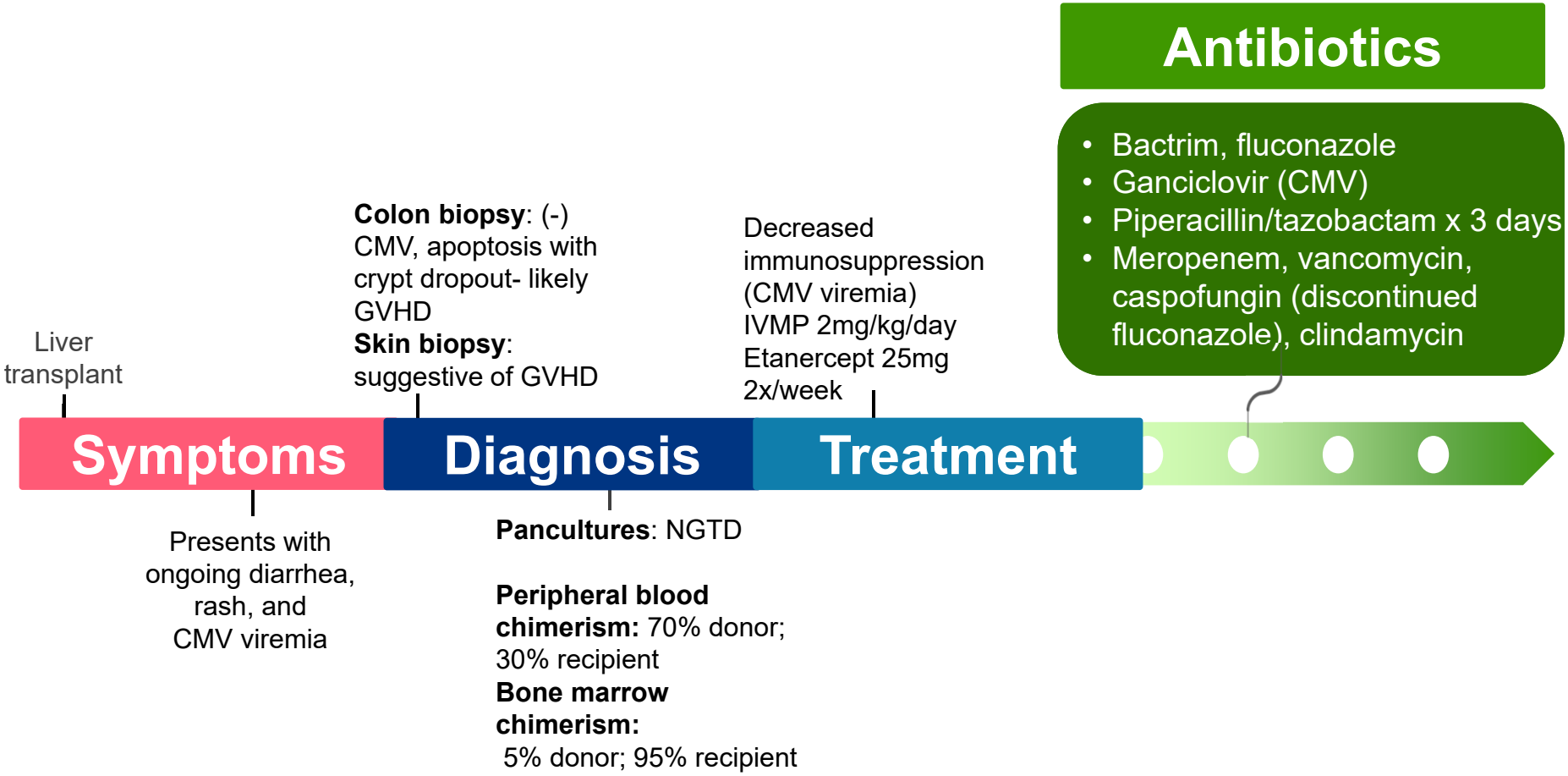
Pneumocystis pneumonia

Consider standard post transplant antibiotics prophylaxis

MAYO CLINIC

Transplantation. 2016; 100(12): 2661–2670
Am J Transplant. 2004; 4: 466–474

AB's Timeline of Events



CMV: Cytomegalovirus
GVHD: graft vs host disease
NGTD: no growth to date
IVMP: intravenous methylprednisolone

When treating GVHD, what was the highest reported cause of infection?

- A) Invasive aspergillosis
- B) Disseminated candidiasis
- C) Enterococci
- D) Enterobacter

Factors Affecting Mortality

Factor	Surviving (n=28)	Dead (n= 59)	P-value
Age, yr	38.7 ± 22.7	40.4± 15.5	0.1
Sex, (male)	20 (71.4)	38 (64.4)	0.8
Rash	27 (96.4)	55 (93.2)	0.8
Fever	17 (60.7)	41 (69.5)	0.1
Pancytopenia	12 (42.9)	35 (59.3)	0.03
Diarrhea	11 (39.3)	36 (61)	0.04
Age difference between D and R (yr)	14.6 ±3.1	22.6 ± 2.7	<0.0001
Time between sx and dx or first treatment, days	13.3 ±2.6	15 ± 2.3	<0.0001

MAYO CLINIC

World J Gastroenterol 2012; 18(37): 5240-5248
Sx: symptoms
Dx: diagnosis

Additional Risk Factor for Mortality?

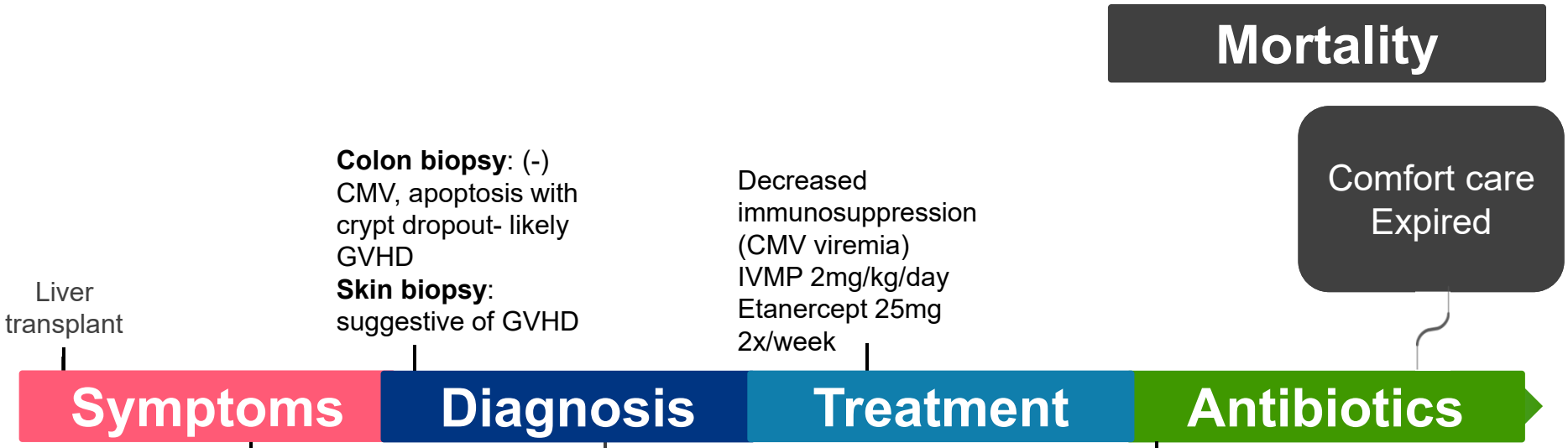
D younger than R >20 yr	Induction/ IS	P-value	Hazard ratio (95% CI)
D younger than R <20 yr	rATG	0.572	0.712 (0.219-2.317)
	Basiliximab	0.152	1.69 (0.825-3.461)
	MMF	0.726	0.895 (0.482-1.663)
D younger than R >20 yr	rATG	0.820	1.096 (0.498-2.408)
	Basiliximab	0.05	1.743 (1-3.038)
	MMF	<0.001	0.418 (0.264-0.662)

Conclusion: avoiding Basiliximab induction and adding Mycophenolate to maintenance regimen may be favorable in those that have a donor >20 years younger

Am J Transplant. 2019; 19 (suppl 3)

rATG: anti-thymocyte globulin
MMF: mycophenolate mofetil
IS: immunosuppression

AB's Timeline of Events



CMV: Cytomegalovirus
GVHD: graft vs host disease
NGTD: no growth to date
IVMP: intravenous methylprednisolone

Summary

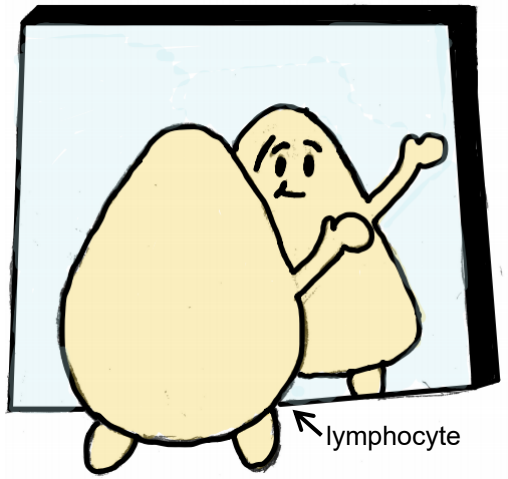
- GVHD is an rare complication after liver transplantation
- GVHD results from T cells of the graft reacting against tissues of the recipient
- Strong treatment recommendations cannot be made based on available evidence
  - High-dose steroids are an important part of first line treatment with a variety of second line options available
  - Broad spectrum antibiotics and antifungal prophylaxis appears reasonable
  - CMV and Pneumocystis prophylaxis is advised during high-level immunosuppression

MAYO CLINIC

CMV: Cytomegalovirus
GVHD: graft vs host disease

MAYO CLINIC

Graft vs Host Disease (GVHD): The Enemy within Me



Stephanie Gore, PharmD, MPH
PGY2 Solid Organ Transplant Resident