Transfusions, etc!

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@bloodman

OHSU GENERAL HEMATOLOGY

DISCLOSURE

Current Relevant Financial Relationship(s)

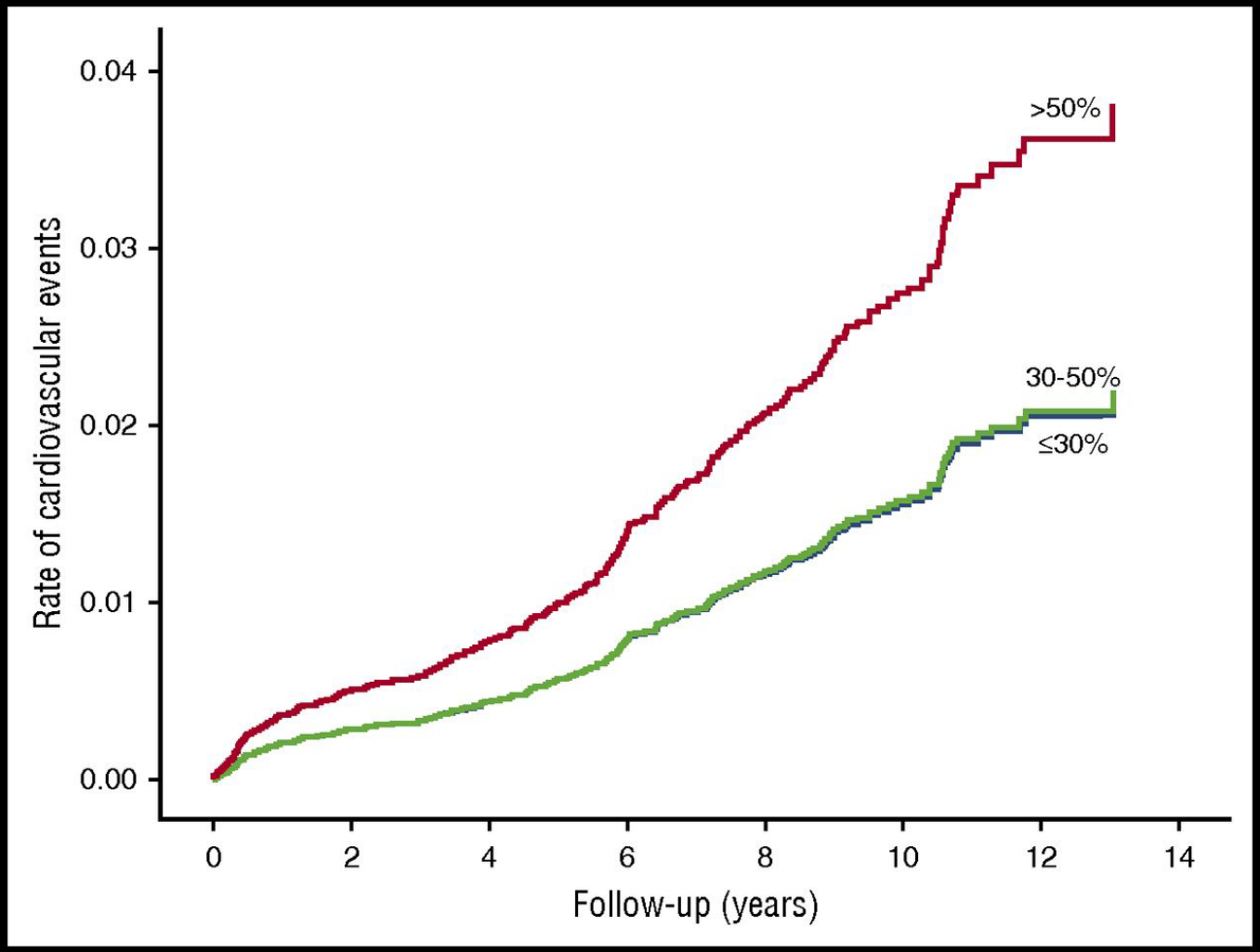
None

Contact Pathway

- Part of coagulation cascade everyone ignores
- Factors 11, 12, prekallikren and HMW Kininogen
- No bleeding 12, prekallikren and HMW Kininogen

Factor 11

- Deficient patients often with mild to no bleeding
- Less arterial and venous disease



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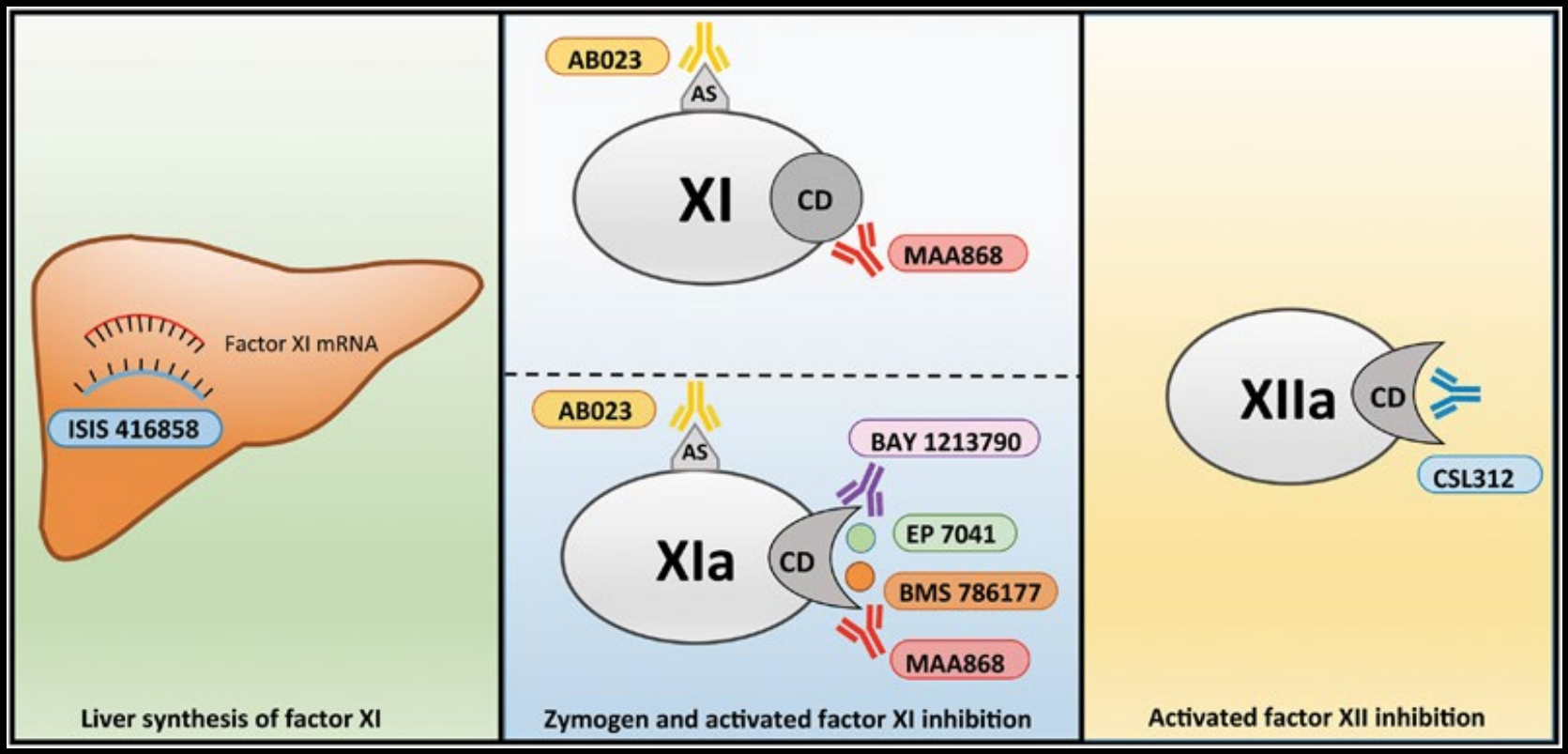
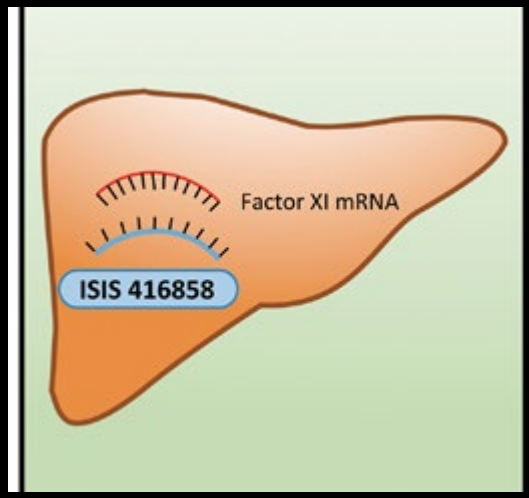
Contact Inhibition

- Contact pathway not need for routine hemostasis
- Blocking pathway in animal models show less thrombosis with no bleeding
- Human studies…


Factor XI mRNA
ISIS 416858
Liver synthesis of factor XI
AB023
AS
XI
CD
MAA868
AB023
AS
BAY 1213790
XIa
CD
EP 7041
BMS 786177
MAA868
Zymogen and activated factor XI inhibition
XIIa
CD
CSL312
Activated factor XII inhibition

FXI-ASO



- Factor 11 antisense
- TKA N= 300
- Drug started 36 days before surgery
  - Days 1, 3, 5, 15, 22, 29, 36
- NEJM 372:232, 2014

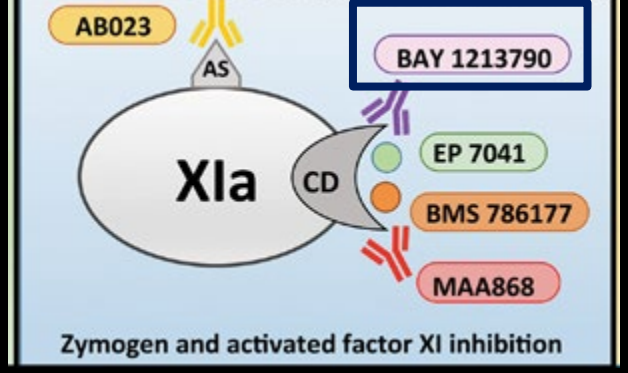
Results

	FXI 200mg	FXI 300mg	Enox 40mg
VTE (%)	36	3	21
Prox DVT (%)	5	1	6
Bleeding (%)	4	2	6
F11 (%)	38	20	93

Bottom Line

- 2 proofs of concept
  - Antisense
  - Lower 11 with less clots and no more bleeding

Osocimab



- Mab binds F11 active site
- 2 phases – TKA N = 813
- Phase 1- day after surgery
  - 0.3, 0.6, 1.2, and 1.8 mg/kg
- Phase 2 – day before surgery
  - 0.3, 1.8 mg/kg
- JAMA 323:130, 2020

Results PostOp

	0.3 mg/kg	0.6 mg/kg	1.2 mg/kg	1.8 mg/kg	Enox 40mg	Apix 2.5 mg
VTE (%)	18	8	13	14	20	12
PDVT (%)	2.6	5.9	3.8	3.8	3.9	2.4
Bleeding	2	0	1	3	6	2

Results - PreOp

	0.3 mg/kg	1.8 mg/kg	Enox 40mg	Apix 2.5 bid
VTE (%)	23	9	20	12
PDVT (%)	6.5	2.5	3.9	2.4
Bleeding (%)	1.9	3.7	5.9	2.0

Milvexian

- Oral F11 inhibitor
- TKA N = 1242
- 6 doses tested
  - BID 25, 50, 100, 200 mg
  - qDay 25, 200mg

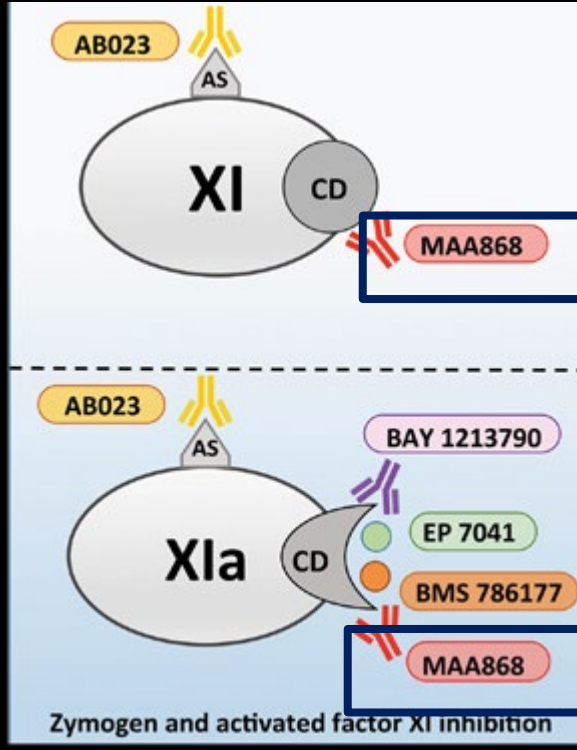
BID Dosing

	25 mg	50 mg	100 mg	200 mg	Enox 40mg
VTE (%)	21	11	9	8	21
PDVT (%)	1	0	1	0	1
Bleeding	1	5	5	3	4

qDay Dosing

	25 mg	50 mg	200 mg	Enox 40mg
VTE (%)	25	24	7	21
PDVT (N)	0	2	0	1
Bleeding (n)	0	5	6	6

Abelacimab



- Mab binds and locks F11 zymogen form
- TKR N = 412
- Drug started 4-6 after surgery
- 30, 75, 150 mg
- NEJM 385:609, 2021

Results

	30 mg	75 mg	150 mg	Enox 40mg
VTE (%)	13	5	4	22
PDVT (N)	1	0	0	2
Bleeding (n)	2	2	0	0

Prophylaxis

- No increased risk of bleeding with blocking F11
- Higher doses more effective than enoxaparin
- Mab just one dose
- Phase III trials underway

Asundexian

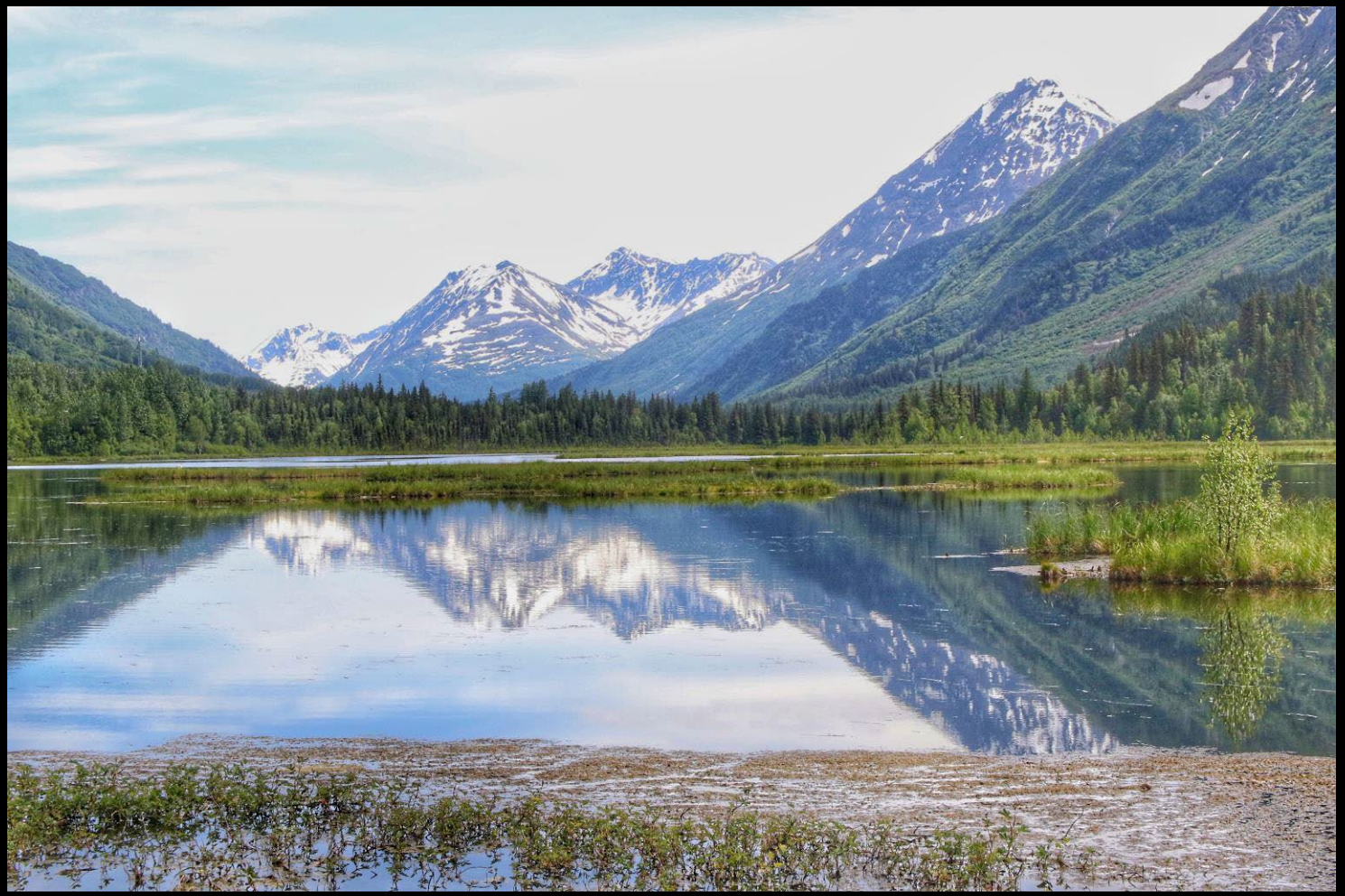
- Oral F11 inhibitor
- Atrial Fibrillation N = 755
- Asundexain 20 or 50mg daily
- Apixaban 5 mg bid
- Lancet 399:1383, 2022

Results

	20 mg	50 mg	Apix
Thrombosis	0.8	1.5	1.2
Bleeding	5	4	10
Major Bleeding	1	1	3

Bottom Line

- Contact pathway promise effectiveness with less bleeding
- Phase III studies underway
- Also effective for “surfaces”
  - Dialysis
  - ECMO
  - VADs



Platelet Refractoriness

I'm not just the president of Hair Club for Men...

Assessing Response To Platelet Transfusions

- Expected increment 15 minutes after Txn:
  - 5 -7,000/uL for each random donor
  - 30,- 50,000/uL for each pheresis

Measure of Transfusion outcome	Formula	Values s/o refractoriness
Absolute Count Increment (ACI)	(Post transfusion plt count – Pre transfusion plt count)	At 60 min ACI ,<5000/cumm after one unit of RDP
Corrected Count Increment (CCI)	$\frac{(ACI \times BSA\ m^2) \times 10^{11}}{\text{No. of plts transfused} \times 10^{11}}$	At 10-60 min <5000/cumm
Posttransfusion Platelet Recovery (PPR)	$\frac{ACI \times \text{Total blood volume} \times 100}{\text{No.of plts transfused}}$	At 60 min <30% At 24hrs <20% (Normal at 1 hr: 67%)

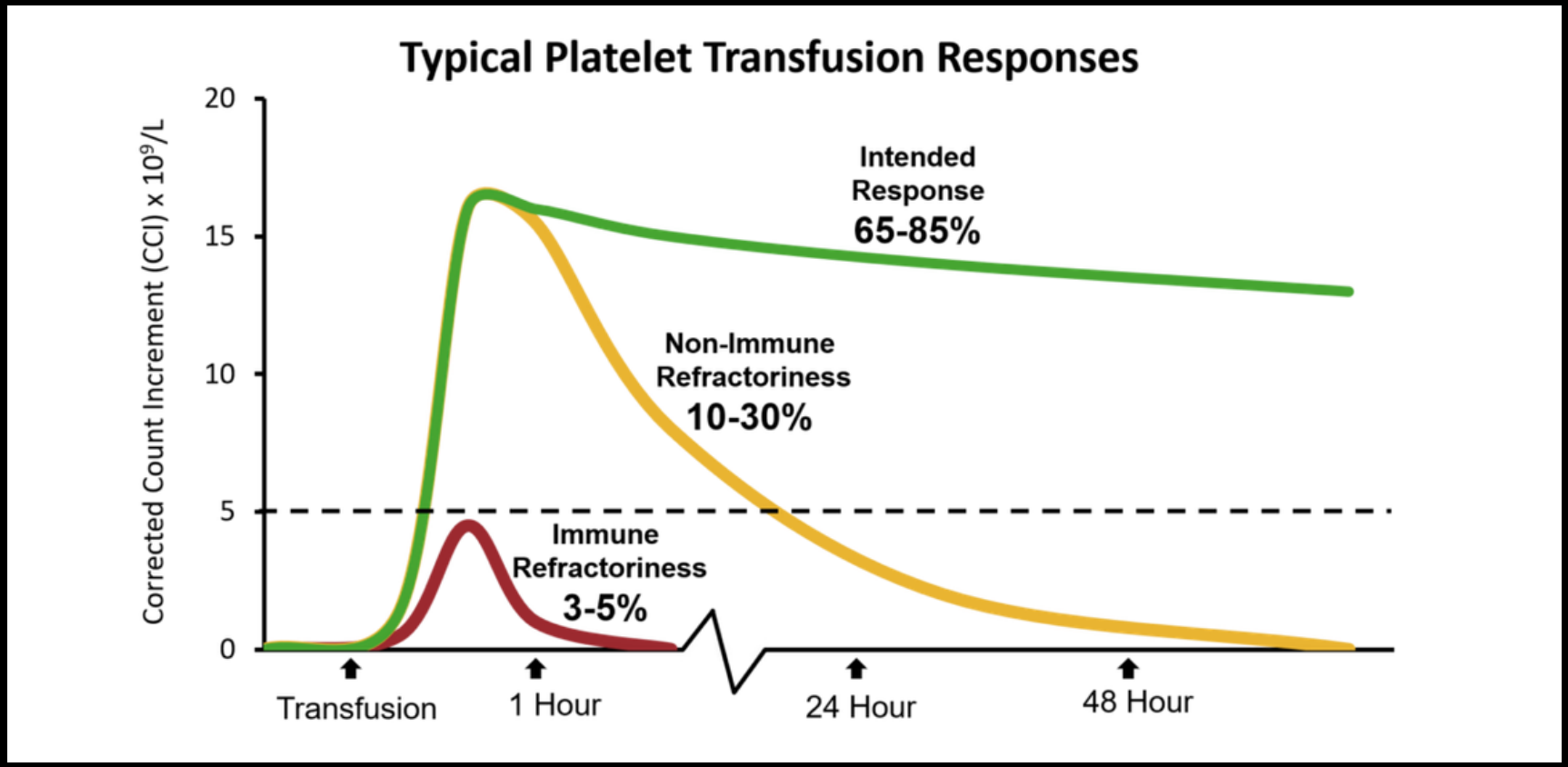
BSA = Body surface area

AABB , Technical manual 16th Edn
Pavenski et al, Tissue antigens 2012

https://slideplayer.com/slide/5795610/

Poor Platelet Response

- Bum product
- Increased consumption
  - Sepsis, bleeding, fever, DIC
- Platelet refractoriness
  - Anti-HLA antibodies, etc.



https://thrombolux.com/platelet-refractoriness-in-hemonc-patients/

Platelet Refractoriness

- Poor/no increment immediately after transfusion
- Only ~ 30% are due to anti-HLA antibodies

Other Cause Of Platelet Refractoriness

- Antiplatelet antibodies
- Heparin induced thrombocytopenia
- Drugs (Vancomycin)
- VOD/liver disease
- Post-transfusion purpura

Anti-HLA antibodies

- Platelets with HLA A and B antigens
- Occurs in
  - Previous pregnancies
  - Previous transfusions
- Some naturally occurring

Anti-HLA antibodies

- Risk factors
  - Pregnancy (32% vs 9%)
  - Disease
    - Higher in aplastic anemia and lower in lymphoid malignances

HLA Alloimmunization

- Occurs in 5-50% of patients
- Leads to profound platelet refractoriness
- Complicate therapy of cancer and surgeries

HLA Alloimmunization

- Does not respond to immunosuppression!
- Many therapies have been tried and found wanting

Diagnosis

- Demonstrate platelet refractoriness
- Demonstrate presence of anti-HLA antibodies

Panel Reactive Antibodies

- Patients serum is tested against a variety of HLA antigens
  - Many methods are used
- Panel Reactive Antibodies (PRA)
  - Based on anti-HLA antibodies and frequency in the population of those HLA antigens

Example of Report

OREGON HEALTH & SCIENCE UNIVERSITY

Oregon Health Sciences University
Immunogenetics & Transplantation Lab
2611 SW 3rd Ave.
Portland, OR 97201
(503) 494-2893

Name: [redacted]
MRN:
DOB:
Category:
Physician:

HLA Antibody Screening Report with MFI

HLA Typing Results:

Name/ID	Relation	A	B	Bw	Cw	DR	DRw	DQB	DQA	DPB
Patient		26	38							
		29	44							

HLA Typings have been done by sequence-specific primers, reported as serological equivalents.

Unacceptable Antigens Assigned in UNOS

HLA Antibody Screening Results:

Sample Date	Sample #	Test	Result	PRA (%)	Specificities
08/11/2019	19892460	LUM ID I	Positive		B:51 53 35 78

Example of Report

MFI values for single antigen specificities identified. MFI values of 1000 and greater are considered as positive.

Sample Date: 08/11/2019 Sample #:19892460

Class I

Antigen	Allele	MFI
B51,Bw4	B*51:01	7994
B51,Bw4	B*51:02	4210
B53,Bw4	B*53:01	4154
B35,Bw6	B*35:01	4114
B78,Bw6	B*78:01	3917

Comments:

Platelet Refractory Panel
Fax Report to OHSU Transfusion Services 503-494-4144
Fax Report to ARC HLA Lab 503-280-1483

Estimated cPRA = 31%, based on >3000 MFI cutoff

Transfusion Strategies

- Sounds simple “Pick product not likely to react”
- Difficult in practice
- Methods
  - HLA matching
  - HLA avoidance
  - Cross-matching

HLA Matched Platelets

- Picking platelet unit match for patients HLA type
- Platelet donors with HLA typing on file
- Can take time

Match grades for HLA-matched platelets

GRADE	ANTIGEN MATCHES
A	4 antigen match
B	2 or 3 antigen match Unmatched antigens are unknown or cross-reactive
B1U	1 antigen unknown or blank
B1X	1 cross-reactive group
B2UX	1 antigen blank and 1 antigen cross-reactive
B2X	2 antigens cross reactive
C	1 mismatched antigen
D	2 or more mismatched antigens

Grade A is the ideal match. Some B grade matches such as B1U or B2U can provide an adequate response, however grade C and D matches do not provide a better

https://slideplayer.com/slide/15371211/

HLA Avoidance

- Picking platelets they don't have implicated HLA antigens
- Faster and can use products off the shelf

Example of Report

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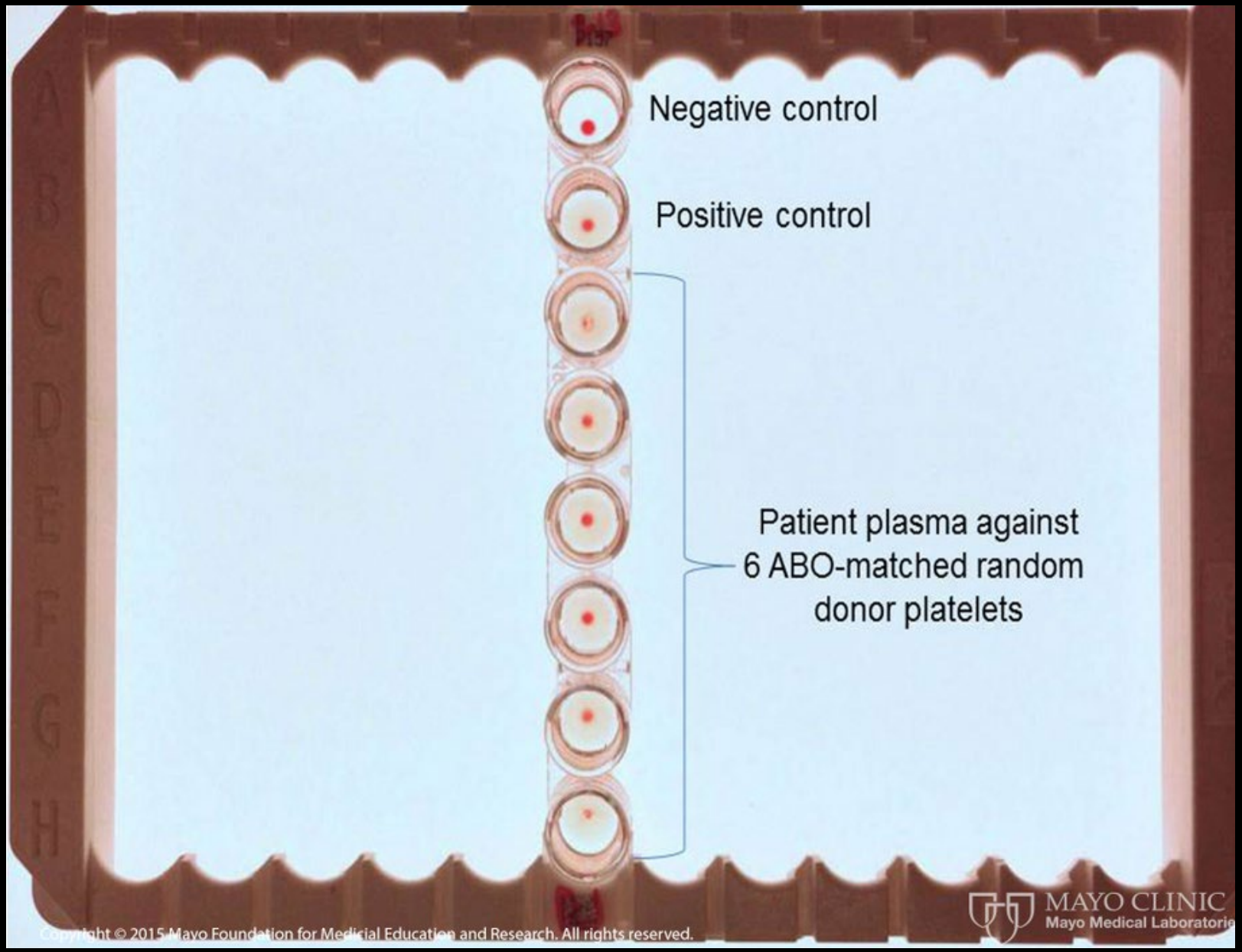
Platelet Crossmatching

- Using patients serum to rule out reacting products
- Can screen a wide number of platelets

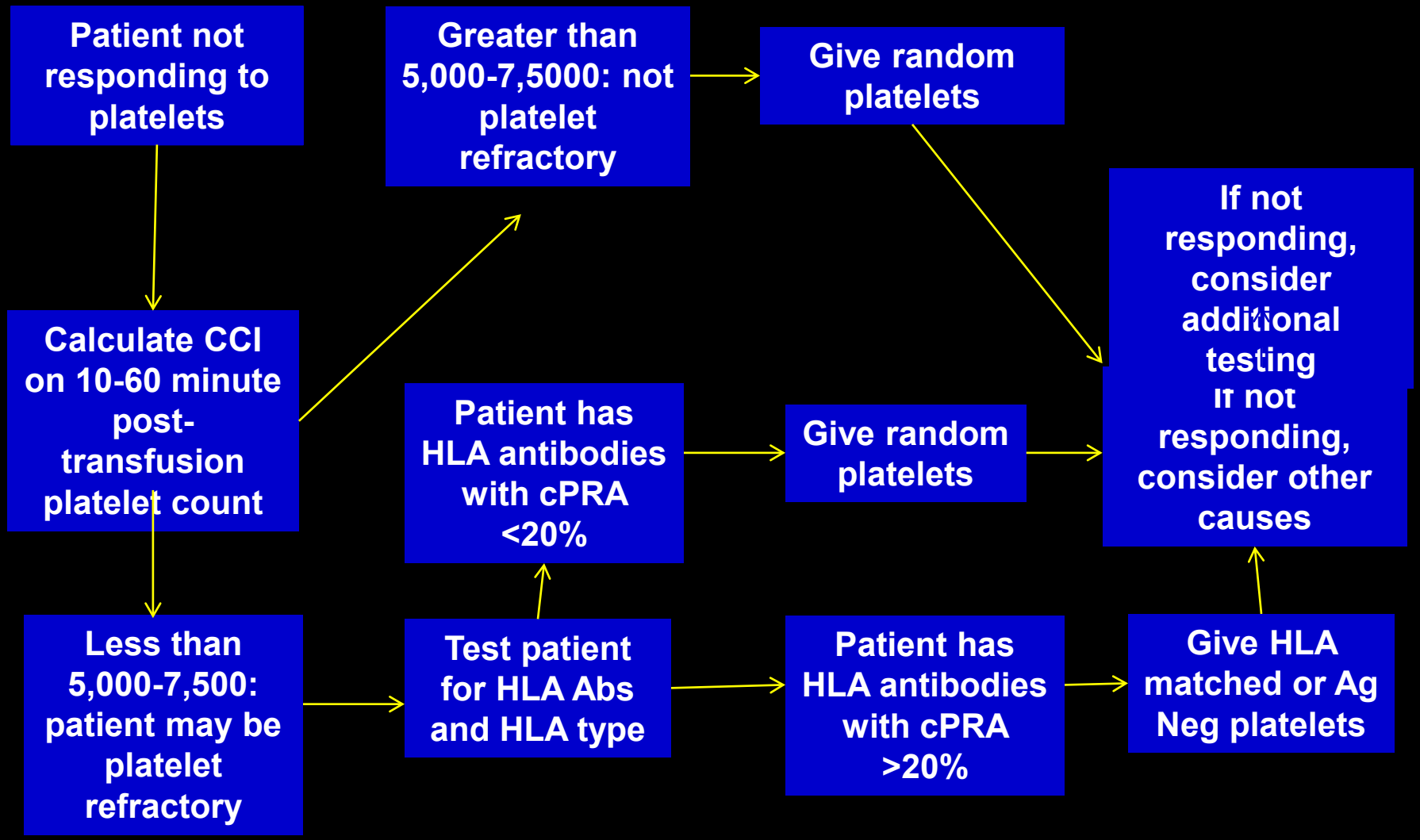


https://news.mayocliniclabs.com/2016/06/28/pathways-062816/

Pros-Cons

- HLA matching
  - Pro: prevents more HLA issues
  - Con: hard to get good matches
- HLA avoidance
  - Pro: more donors
  - Con: risk more antibodies
- Cross matching
  - Pro: rapid
  - Con: risk of more antibodies

Work Flow at OHSU



Really Refractory

- Review for “good” donors
- Consider family members
- Review if other causes of refractoriness

Heroic Therapy

- Platelet drips
  - One unit over 6 hours
- High dose IVIG
  - 1 gram/kg twice weekly
- Plasmapheresis
- rVIIa
- TPO-agonists

Platelet Drips

- Minimal rise in platelets
- But cessation of bleeding
  - Some platelets survive for hemostasis
- Anecdotal
- Clinical trial underway

IVIG

- May improved 1 hours increment
- No effect on 24 hours
- Negative clinical trials
- Not recommended

rVIIa

- Recombinant factor VIIa effective in some platelet disorders
- Use is anecdotal
- Consider if life-threating bleeding

Platelet Growth Factors

- Not effect for chemotherapy
- Can be consider in thrombocytopenic liver patients before transplant

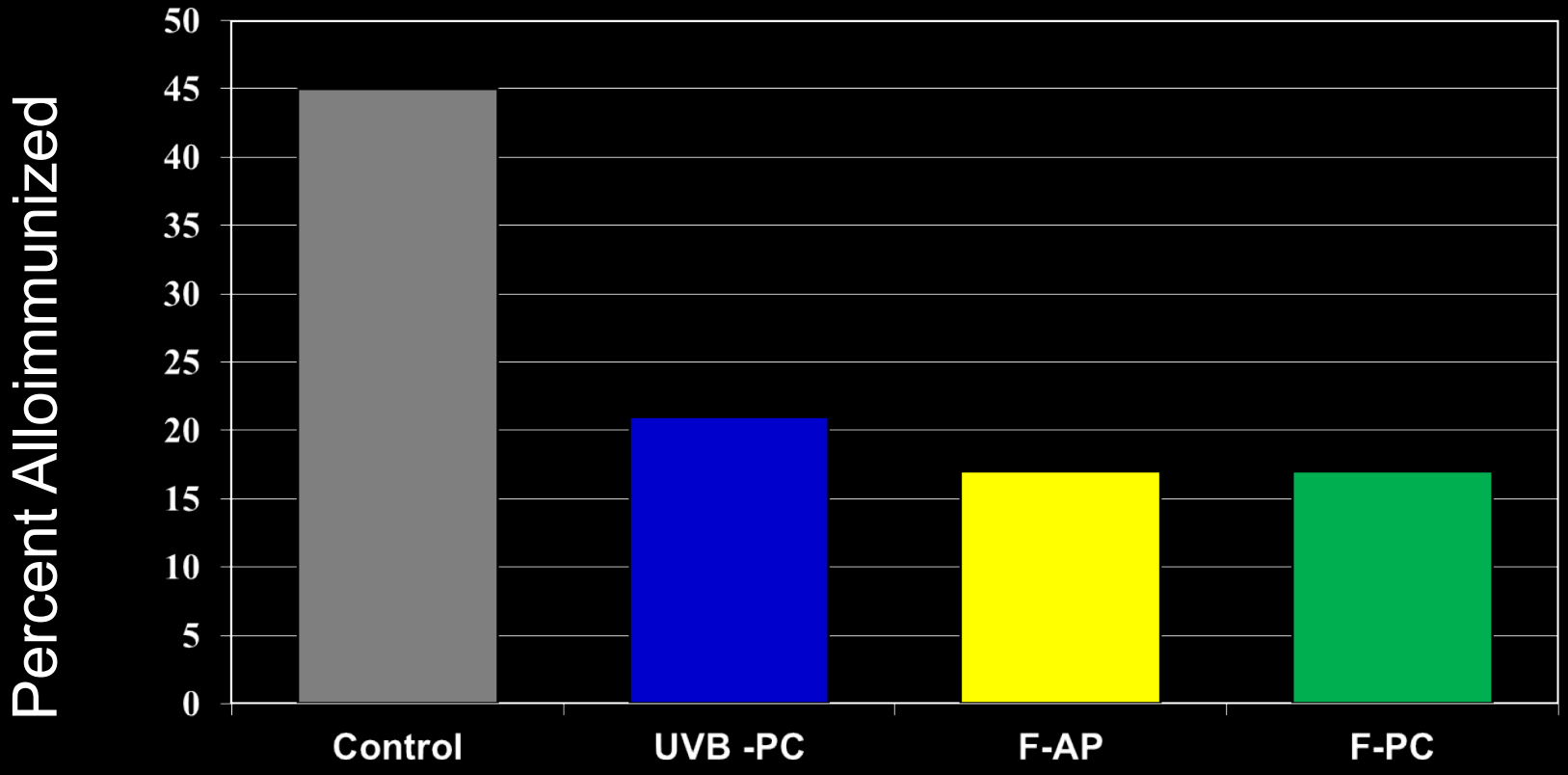
Others

- Plasmapheresis
  - Risky
- Eculizumab
  - ~ 50% response rate in small study
  - Very expensive and minimal data

Prevention!

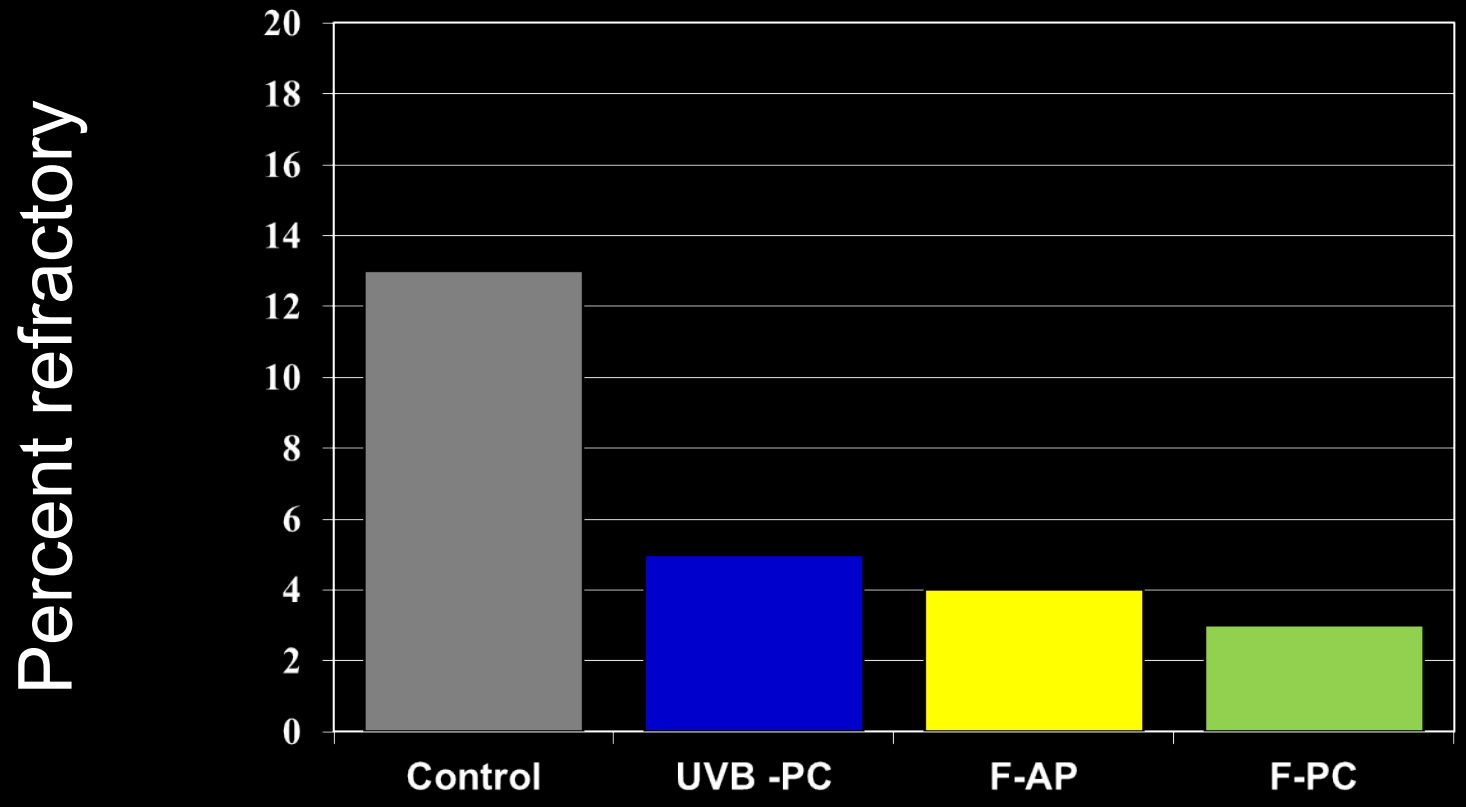
- Need white cells plus platelets to get alloimmunization
- Leukodepletion markedly reduces alloimmunization

TRAP Trial: Alloimmunization



New Eng J Med 1997; 337:1861-9

TRAP: Refractoriness



New Eng J Med 1997; 337:1861-9.

Leukoreduction

- Prestorage for all blood products
  - > 70% reduction in alloimmunization
- Not perfect to prevent all alloimmunization
  - Pregnancy
  - Spontaneous
  - Even with leukoreduction some patients become alloimmunization

Platelet Refractoriness

- Consumption vs immune destruction
- Prevention is key
- Difficult clinical issue