Case-Control Study: ABO-Incompatible Plasma Causing Hepatic Veno-Occlusive Disease in HSCT

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3/7/13

Outline

- Background
  - VOD
  - ABO expression
  - VOD and Platelet transfusion
- Study
  - Methods
  - Patient Population
- Conclusions
- Future Directions

Hematopoietic Stem Cell Transplant

- Reconstitute bone marrow after high-dose chemotherapy
  - Allogeneic or autologous
  - Sources: cord, bone marrow, peripheral
  - Diseases: leukemia, lymphoma, solid organ tumors
- Pediatrics: Improved prognosis in solid organ tumors refractory to conventional treatment
  - High-dose chemo with stem cell rescue

Complications of High-Dose Chemo and HSCT

- Graft versus host disease (GVHD)
- Graft rejection
- Disease relapse
- Anemia
- Neutropenia and infection
- Hepatic veno-occlusive disease
- Thrombocytopenia

Hepatic Veno-Occlusive Disease (VOD)

- Syndrome occurring after high-dose chemotherapy followed with HSCT
  - Signs and Symptoms:
    - Jaundice (bilirubin > 2 mg/dL)
    - Painful hepatomegaly
    - Fluid retention (weight gain > 5%)
    - + Doppler evidence of decreased or reversed portal blood flow
- Occurs ~10% after allogeneic SCT with myeloablative therapy
  - Less for autologous and reduced intensity conditioning regimens

Table I **Clinical criteria for the diagnosis of VOD**

(Modified) Seattle criteria

Presence before day 20 after stem cell transplantation (SCT) of at least two of the following:

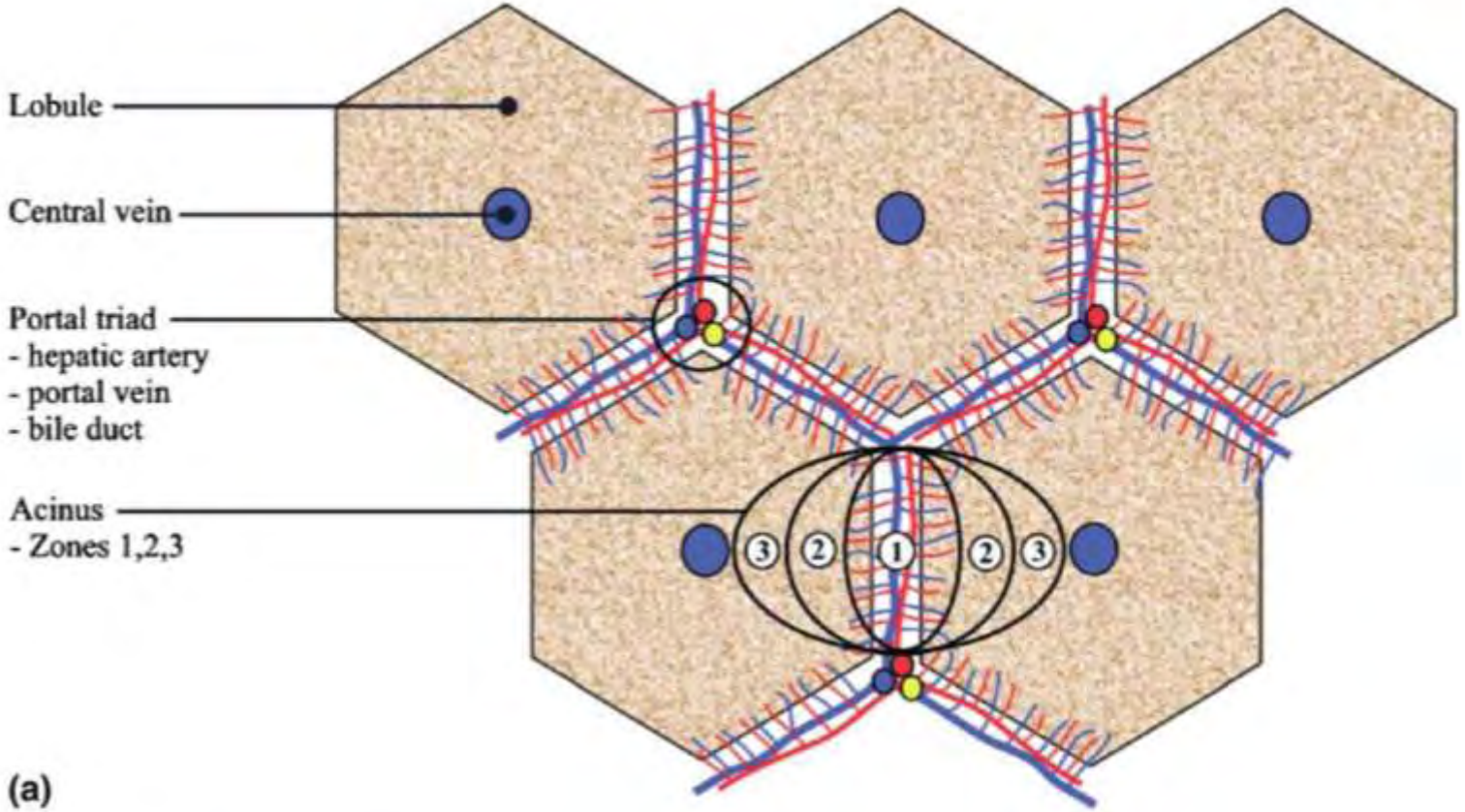
- Bilirubin $\geqslant$2 mg/dl ($\approx$34 μmol/l)
- Hepatomegaly, right upper quadrant pain
- Ascites +/– unexplained weight gain of >2% baseline

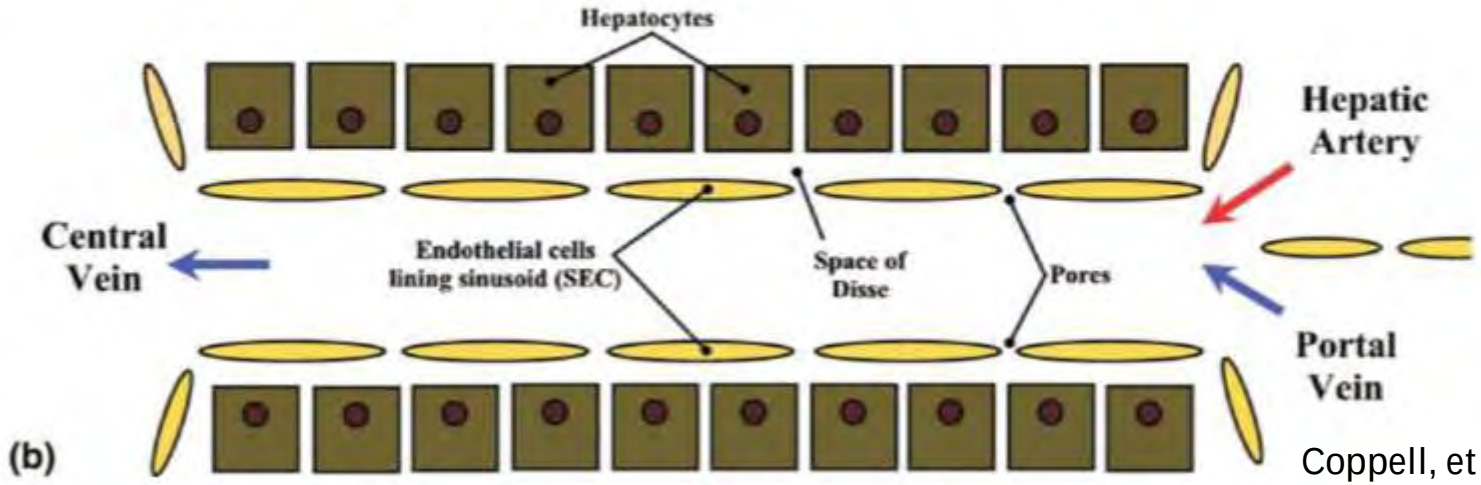
Baltimore criteria

Hyperbilirubinaemia $\geqslant$2 mg/dl before day 21 after SCT and at least two of the following:

- Hepatomegaly (usually painful)
- Ascites
- Weight gain >5% from baseline

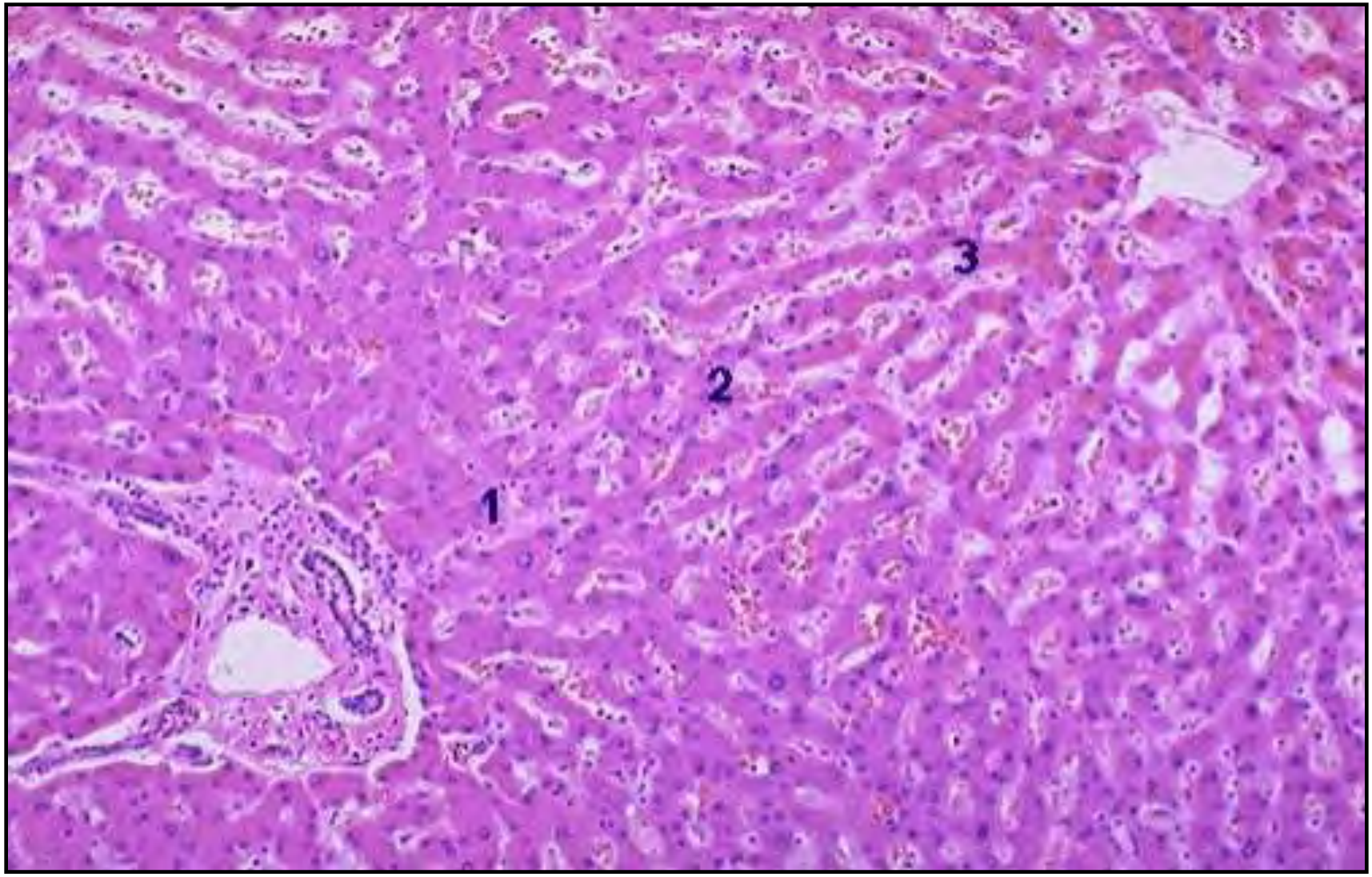
Coppell, et al. Blood Review 2003;17,63-70.





Coppell, et al. Blood Review 2003;17,63-70.

Liver Histology 101

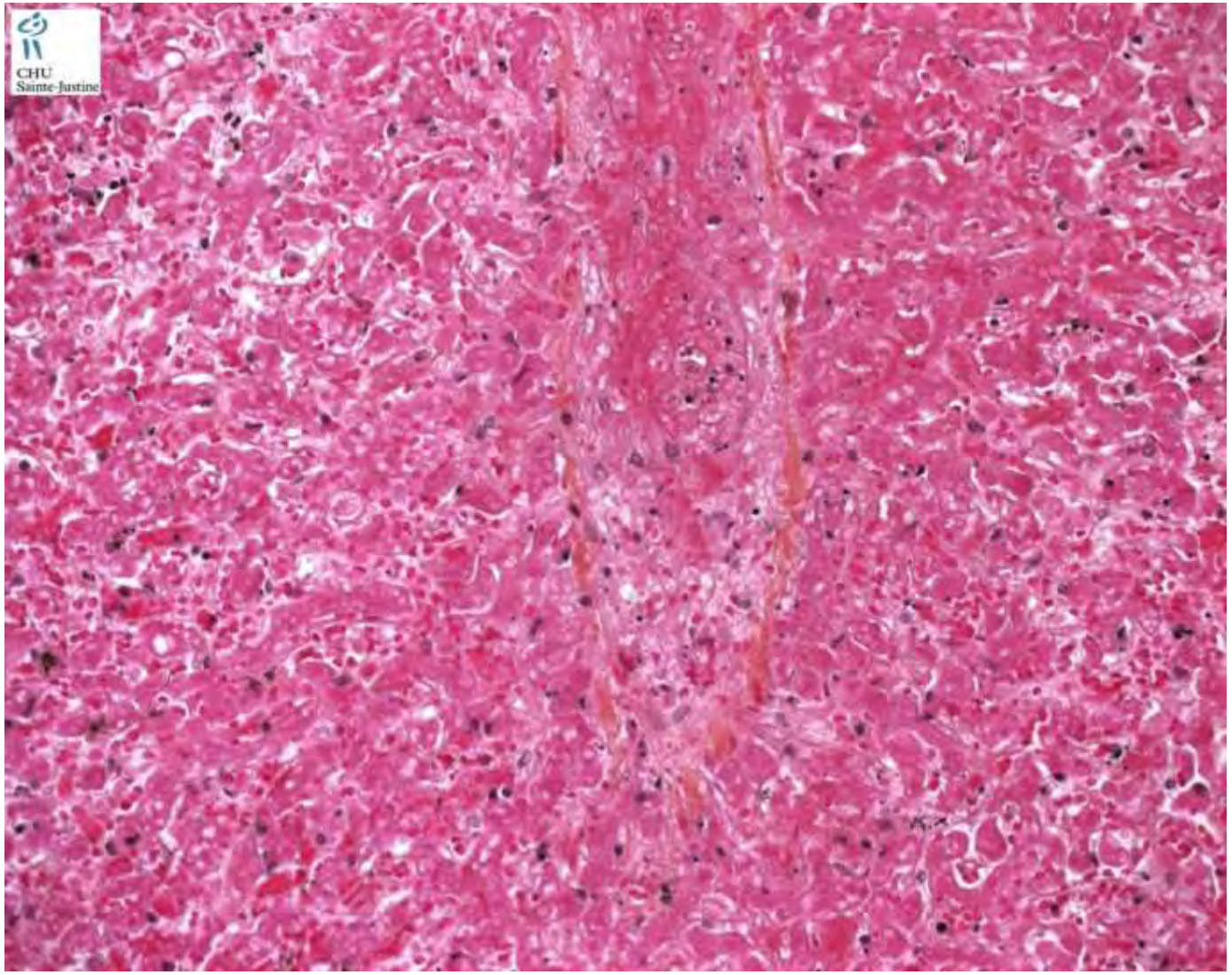


http://library.med.utah.edu/WebPath/LIVEHTML/LIVER003.html

HVOD

- Mortality ranges 67% to 90% (severe VOD)
- Rename sinusoidal obstruction syndrome (SOS)
  - Primary site of injury: hepatocytes and sinusoidal endothelial cells (SEC) in zone 3
    - Murine models: damage to SEC early
      - Edema, fibrin, and fragmented red cells fill subendothelial zone
      - Narrowing of venules and sinusoids
      - Late: lumens obliterated by fibrosis
- Data suggests that depletion of glutatione by conditioning drugs is a risk factor

Liver



http://www.humpath.com/spip.php?article8718

Risk Factors for VOD

- Pre-existing liver damage
- Previous SCT
- Conditioning regimen and cytotoxic therapy
  - Busulfan, cyclophosphamide, dacarbazine
- Type of transplant
- Genetic factors – glutathione deficiency
- ABO plasma incompatible platelet transfusion???

Platelet Transfusion Containing ABO-Incompatible Plasma and Hepatic Veno-occlusive Disease after Hematopoietic Transplantation in Young Children

Valérie Lapierre,[1,4,5] Cédric Mahé,[2] Anne Aupérin,[2] Férial Stambouli,[3] Nadia Oubouzar,[1] Dominique Tramalloni,[1] Ellen Benhamou,[2] Pierre Tiberghien,[4] and Olivier Hartmann[3]

- Plasmatic ABO incompatibility (minor) exists in blood products with infusion of anti-A or anti-B
  - Such antibodies could bind to endothelial cell A or B antigens
  - Could result in:
    - Endothelial cell damage
    - Procoagulant activity
- Investigate the role of ABO-incompatible plasma in platelet concentrates and occurrence of HVOD (main endpoint)

Transplantation 2005;80: 314–319

Tissue distribution of histo-blood group antigens

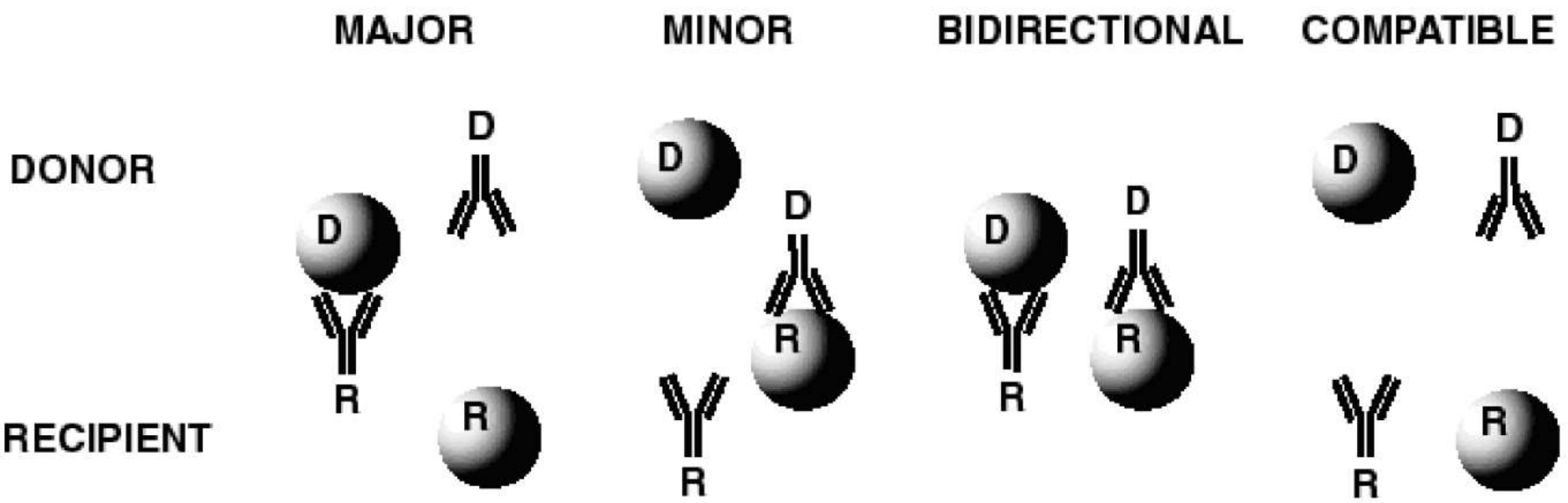
Review article

VIBEKE RAVN[1] and ERIK DABELSTEEN[2]

[1]Department of Pathology, Herlev University Hospital, Denmark
[2]School of Dentistry, Faculty of Health Sciences, University of Copenhagen, Denmark

Vascular endothelium expresses ABH antigens irrespective of the secretor status and mainly carried by type 2 chains. Expression of ABH and related antigens is inconstant, and is among other, mainly unknown, factors related to the ABH erythrocyte blood type. ABH and related antigens are differentiation markers for *haematopoietic cells*.

ABO Incompatibility



Szczepiorkowski ZM. Transfusion support for hematopoietic transplant recipients. In: Roback JD, Combs MR, Grossman BJ, Hillyer CD, eds. Core principles in cellular therapy. Bethesda, MD: AABB, 2008:73-90.

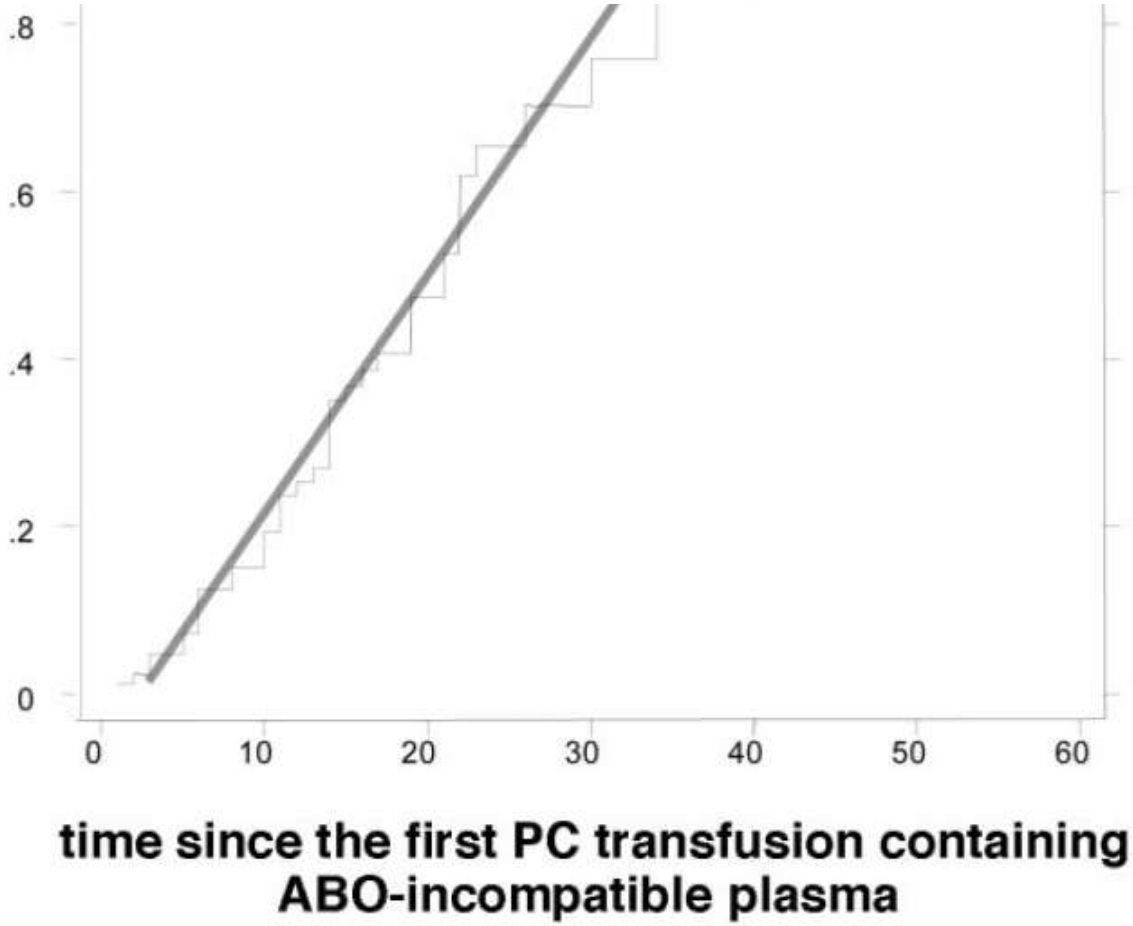
- 186 young children at a single institution (Jan 1988 – Jan 1999)
- High risk of developing HVOD due to busulfan-containing conditioning regimens and single autologous HSCT

TABLE 1. Population characteristics

Characteristic	Median (range) or n (%)
Age (years)	4 (0.75–17)
Diagnosis	
Neuroblastoma	112 (60)
Brain tumor	74 (40)
Medulloblastoma	45
Malignant brain stem glioma	15
Ependymoma	10
High grade astrocytoma	4
Body weight (kg)	15 (8–61)
Sex	
Girls	78 (42)
Boys	108 (58)
Blood type	
O	81 (44)
A	78 (42)
B	22 (12)
AB	5 (2)
Number of platelet concentrate transfusions per week	2.4 (0.4–5.5)
Proportion of pooled random donor platelet concentrates (%)	89 (0–100)
Cyclophosphamide in the conditioning regimen	
No	121 (65)
Yes	65 (35)
Days between conditioning regimen initiation and platelet concentrate transfusion containing ABO-incompatible plasma	15 (0–35)

Results

- 73 of 186 kids developed HVOD at median time of 27 days (r 14-52) after initiation of conditioning regimen
- ABO plasma (minor) incompatible PC were transfused in 47% (87/186) of all kids
  - HVOD occurred in 42 of 87 who received at least 1 ABO minor PC **versus** 31 of 99 (31%) who always got ABO compatible PC (P=0.02)



- Nelson-Aalem cumulative hazard/incidence method
- Transfusion of PC with ABO-incompatible plasma was associated with a significant increase in risk of HVOD occurrence:
  - RR 1.95, 95% CI 1.22-3.11, P=0.003

Our Case-Control Study

- **Hypothesis:** transfusion of platelet concentrates with ABO-incompatible plasma is not a risk factor associated with the occurrence of HVOD.

- **Method:** searched Hematopoietic Stem Cell transplant database at the Children's Hospital, Boston:
  - **Cases**: patients who received high dose cytoreductive therapy followed by HSCT who were either diagnosed with HVOD and/or who received treatment with defibrotide in the last 10 years.
  - **Controls:** HSCT patient group without HVOD matched for age, primary malignancy and the type of transplant and conditioning regimen

- **Retrospective data review**: HSCT database and the blood bank database were used to obtain clinical information including:
  - treatment, outcomes
  - ABO typing and compatibility.

Case-Control Study

- 30 children total for 7 matched pairs
  - Age
  - Diagnosis
  - Type of transplant
  - Type of conditioning regimen
- Study Time Frame: 30 days prior to diagnosis of HVOD to 30 days after diagnosis of HVOD
  - Date, number and ABO type of platelet, PRBC and FFP transfusions
  - The time between date of HSCT and date of diagnosis of HVOD in the case was applied to the matched control to calculate day zero in the control group. (Day zero = Date of HSCT + time to HVOD).
- Follow-up period for mortality: 2 to 10 years

	Case (n=15)	Control (n=15)
Age in years (mean, SD)	4.24 ±2.9	5.66±3.9
Sex	34% (5) females 66% (10) males	47% (7) females 53% (8) males
Original ABO Blood Type	O: 6 (40%) A: 8 (53.3%) B: 1 (6.7%) AB: 0	O: 8 (53.3%) A: 4 (26.7%) B: 1 (6.7%) AB: 2 (13.3%)
Underlying Diagnosis	HLH: 3 (20%) Medulloblastoma: 2 (13%) ALL: 3 (20%) AML: 1 (6.8%) PNET: 1 (6.8%) CML: 1 (6.8%) JML:1 (6.8%) Beta-thalassemia major:1 (6.8%) Neuroblastoma: 2 (13%)	HLH: 3 (20%) Medulloblastoma: 2 (13%) ALL: 3 (20%) AML: 2 (13 %) PNET: 1 (6.8%) CML: 1 (6.8%) Beta-thalassemia major:1 (6.8%) Neuroblastoma: 2 (13%)
Auto Stem Cell (%)	34% (5)	34% (5)
Allo Stem Cell (%)	66% (10)	66% (10)
Mobilization Protocol containing: busulfan cyclophosphamide melphalan	60% (9)	60% (9)
Mortality (at 2-10 year follow-up)	7 alive (46.7%) 8 deceased (53.3%)	12 alive (80 %) 3 deceased (20%)

30 Days Before VOD Diagnosis

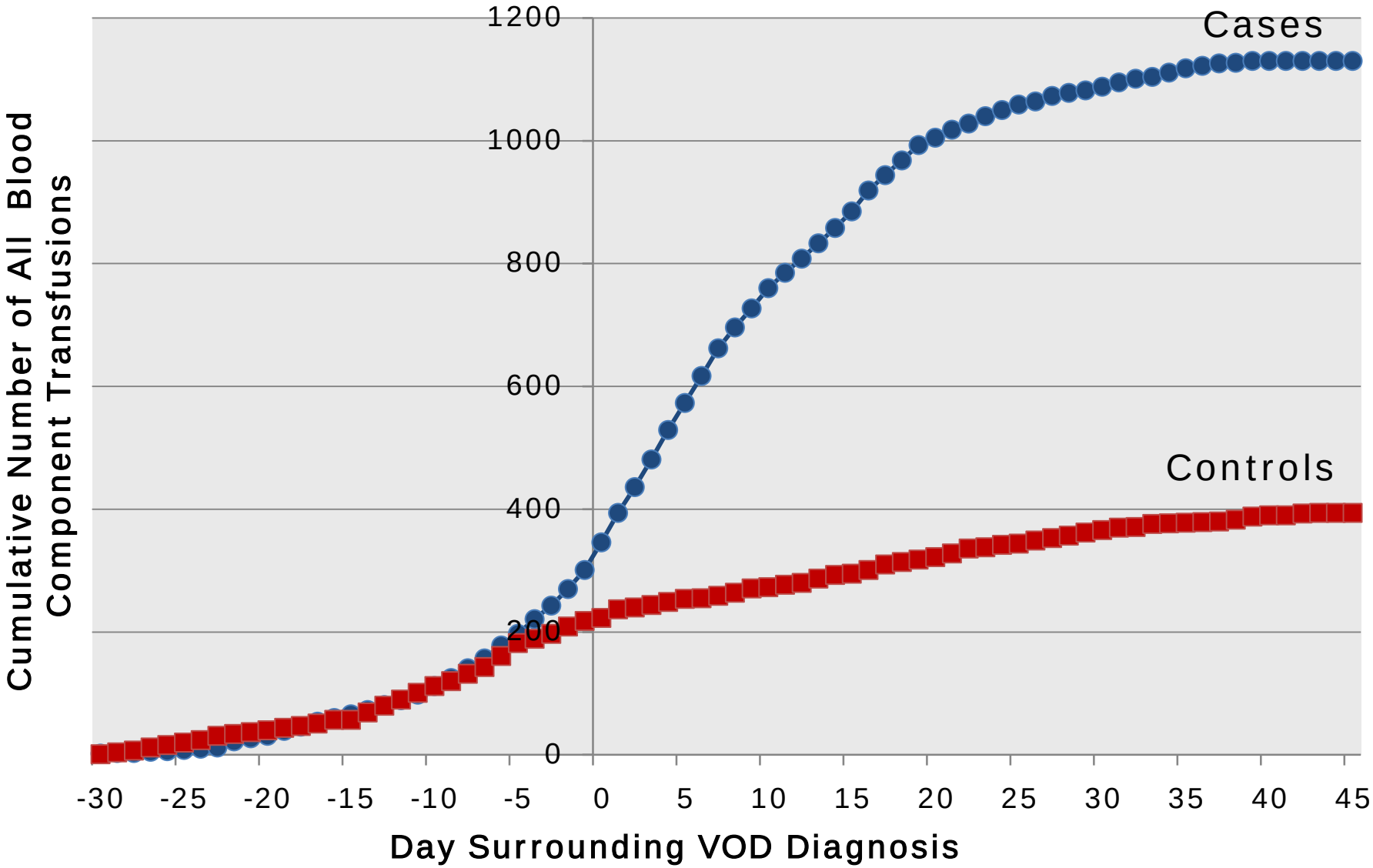
	Cases (Cumulative no. of transfusions)	Controls (Cumulative no. of transfusions)	Cases (Median no. of transfusions	Controls (Median no. of transfusions	p value
Platelet concentrates with ABO-incompatible plasma	19	15	0	0	0.80
Platelet concentrates with ABO-compatible plasma	192	127	12	7	0.11
PRBCs	98	76	5	5	0.71
FFP	37	5	0	0	0.24

30 Days After VOD Diagnosis

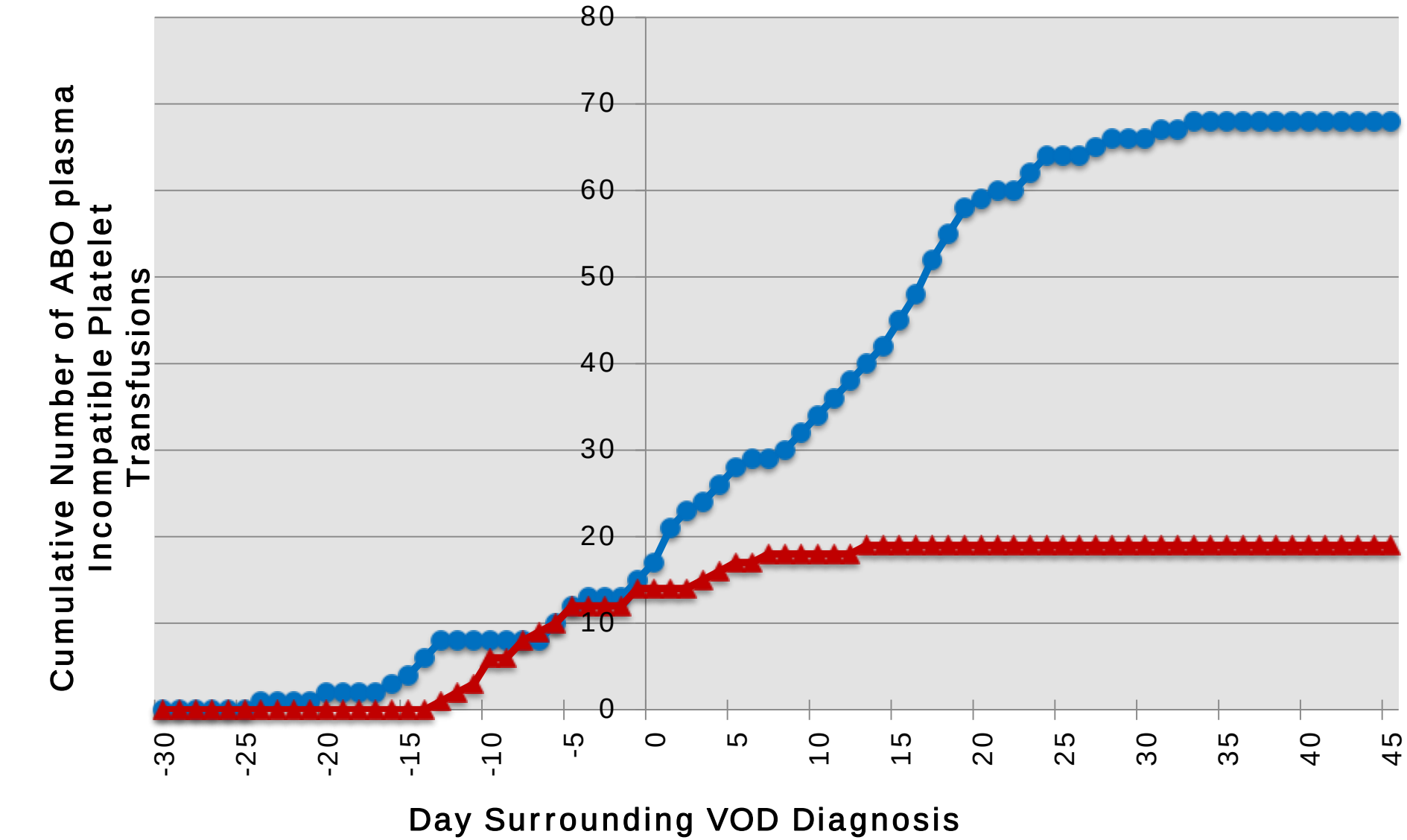
	Cases (Cumulative no. of transfusions)	Controls (Cumulative no. of transfusions)	Cases (Median no. of transfusions	Controls (Median no. of transfusions	p value
Platelet concentrates with ABO-incompatible plasma	77	21	3	0	0.008
Platelet concentrates with ABO- compatible plasma	520	208	19	1	0.003
PRBCs	221	114	8	2	0.003
FFP	270	23	13	0	0.003

		Pre-VOD Diagnosis						Post-VOD Diagnosis					
		Mean	SD	Median	IQR	Range	P Value	Mean	SD	Median	IQR	Range	P value
Incompatible Platelet Transfusions	Case	1.1	1.8	0	2.5	0-5	0.81	3.8	4.4	3	5	0-14	0.008
	Control	1.0	1.3	0	2	0-3		0.5	1.6	0	0	0-6	
Compatible Platelet Transfusions	Case	12.2	8.7	12	7.5	0-36	0.11	22.7	10.6	19	12.5	8-42	0.003
	Control	8.4	5.7	7	9	1-19		5.5	9.9	1	6	0-35	
Compatible RBC Transfusions	Case	5.3	3.9	5	3	0-17	0.71	9.1	6.8	8	7.5	1-24	0.003
	Control	4.6	1.4	5	2.5	3-7		2.6	3.5	2	3.5	0-12	
Compatible FFP Transfusions	Case	1.4	2.6	0	1.5	0-9	0.24	17.0	19.5	13	13.5	0-74	0.003
	Control	0.3	0.9	0	0	0-3		1.1	3.9	0	0	0-15	

All Blood Component Transfusions

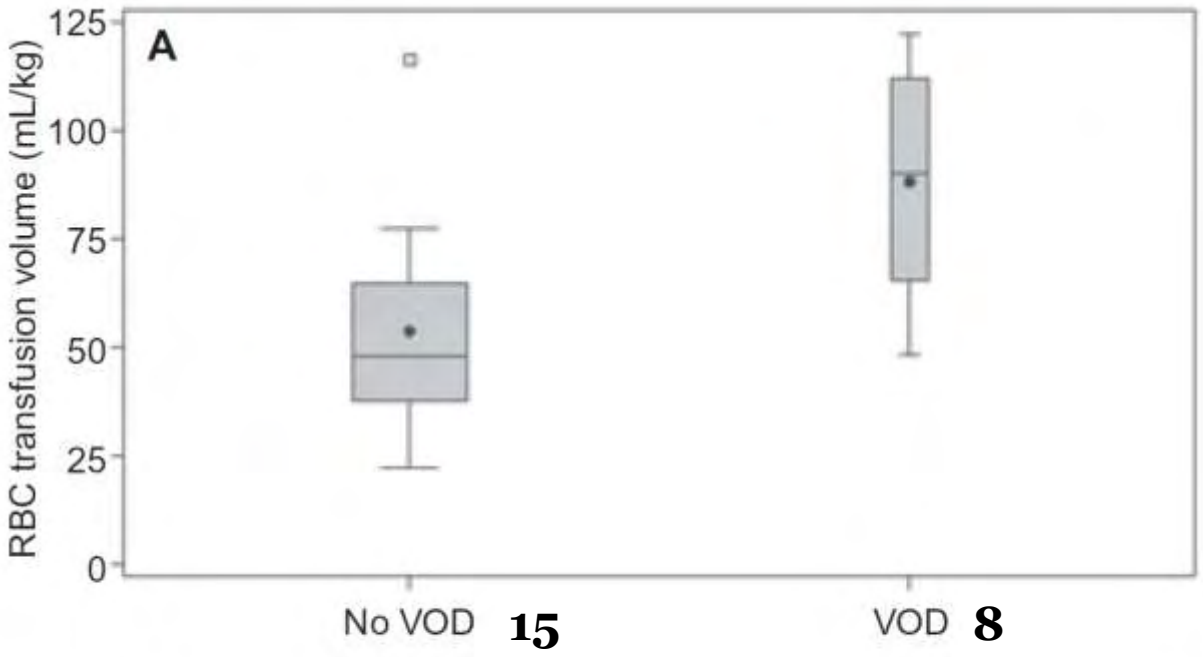


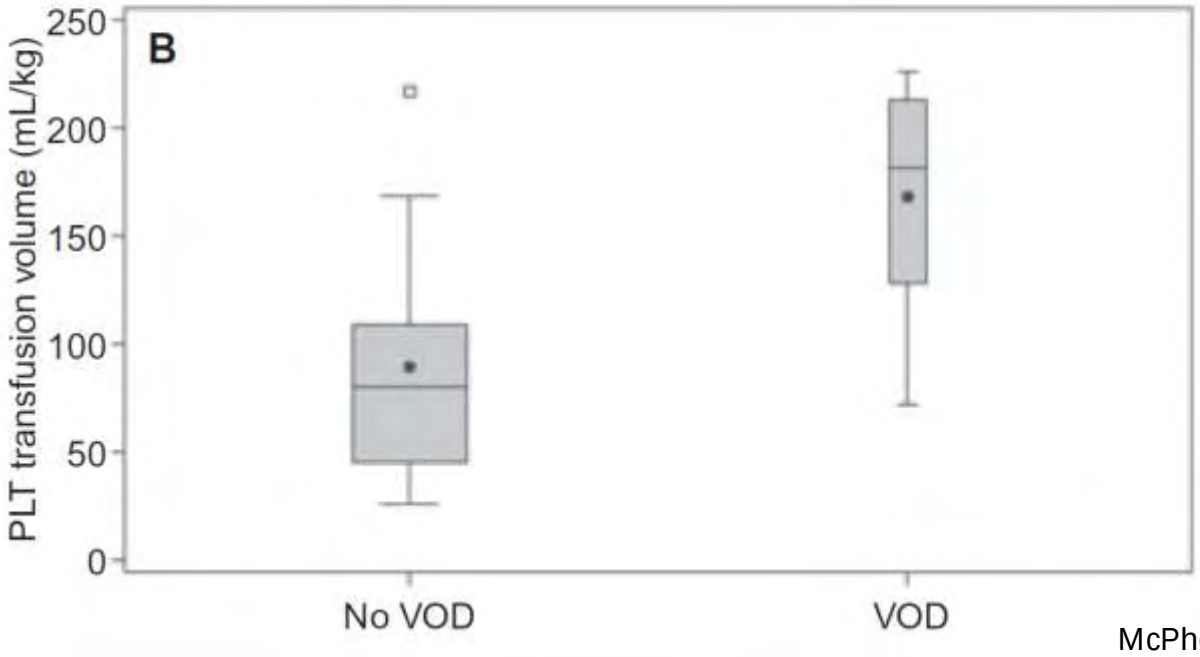
ABO Plasma-Incompatible Platelet Transfusions



Results Summary

- There was no statistically significant difference between the cases and controls in terms of the number of transfusions of the blood components before the development of HVOD
  - All blood components
- The number of transfusions increased significantly in the HVOD group (cases) after the diagnosis of HVOD as compared to the control group.
  - For all blood components!!





McPherson, et al. Transfusion 2009;49:1997-1986.

Conclusion

- In our case-control study, ABO incompatible PC transfusions were not associated with an increased incidence of VOD
  - BUT.....
    - Small N
    - Consistent diagnosis of VOD – criteria for discerning
    - Blood type?

Caveat/Future Direction: ABO Blood type?

- **Cases**
  - 1 Group B
  - 8 Group A
  - 6 Group O
- **Controls**
  - 1 Group B
  - 2 Group AB
  - 4 Group A
  - 7 Group O

Patient and Donor Isohemagglutinin titers??

Tissue distribution of histo-blood group antigens

Review article

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[1]Department of Pathology, Herlev University Hospital, Denmark
[2]School of Dentistry, Faculty of Health Sciences, University of Copenhagen, Denmark

Tissue/embryonic origin	Expression chain type	Layer/ cell type	Carbohydrate expression
Liver, adult (Endoderm)		hepatocytes	none
		sinosoidal endoth.	none
		bile canaliculi	none
	Ty1, Ty2, Ty3	bile ductules	Le^Y, Le^a, (Le^b)
			S-Lc_4*?, Lc_4
		ducts<medium	SLe^a,Le^a, Le^b, Le^Y
		ducts>medium	A/B, H, Le^Y**, ALe^b, ALe^Y
			Tn_{cyt}, T_{cyt}
			Le^a, Le^b, SLe^a

Alterations of platelet function and clot formation kinetics after in vitro exposure to anti-A and -B

Majed A. Refaai, Jessie Carter, Kelly F. Henrichs, Donna C. Davidson, Stephen J. Pollock, Ann E. Casey, Sherry L. Spinelli, Richard P. Phipps, Charles W. Francis, and Neil Blumberg

TRANSFUSION 2013;53:382-393.

- In vitro Plt function of normal platelets of all ABO before and after incubation with:
  - Normal Saline
  - ABO identical plasma samples
  - O plasma with varying titers of anti-A or anti-B
  - Looked at:
    - Plt aggregation
    - Clot kinetics
    - Thrombin generation
    - Plt cytoskeleton function

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- Exposure of antigen bearing platelets to O plasma with moderate to high titers of anti-A/B significantly:
  - Inhibits aggregation
  - Prolongs PFA-100 epinephrine closure time
  - Disrupts clot formation kinetics
  - Accelerates thrombin generation
  - Reduces total thrombin productions
  - Alters platelet cytoskeleton function
  - Influences proinflammatory and prothrombotic
  - Mediator release

Questions Please!

"In the current donor crisis, we've had to be somewhat resourceful with your bone marrow transplant."