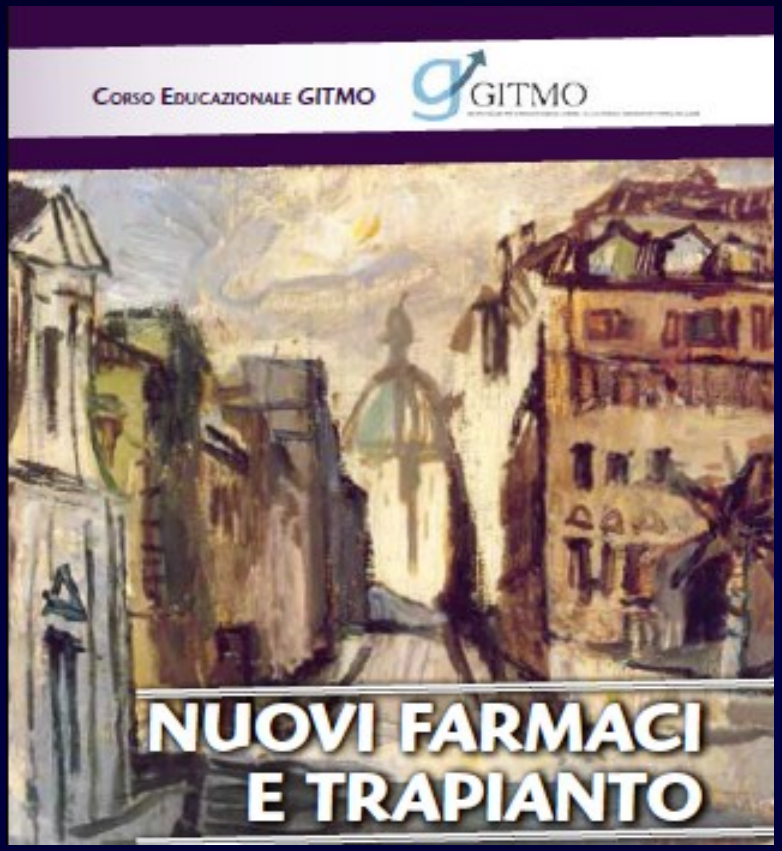
Nuovi farmaci nella terapia delle complicanze endoteliali del trapianto

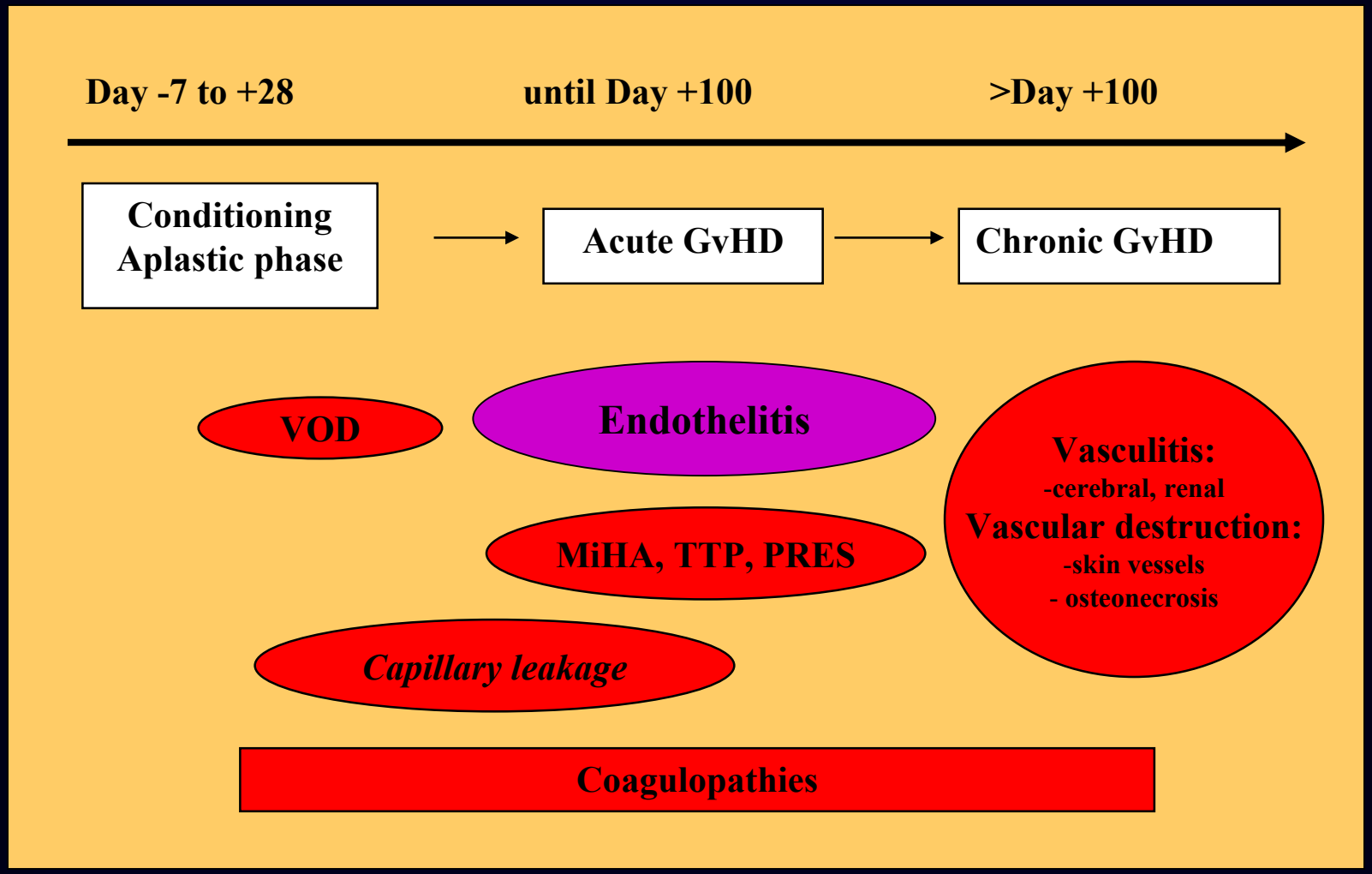


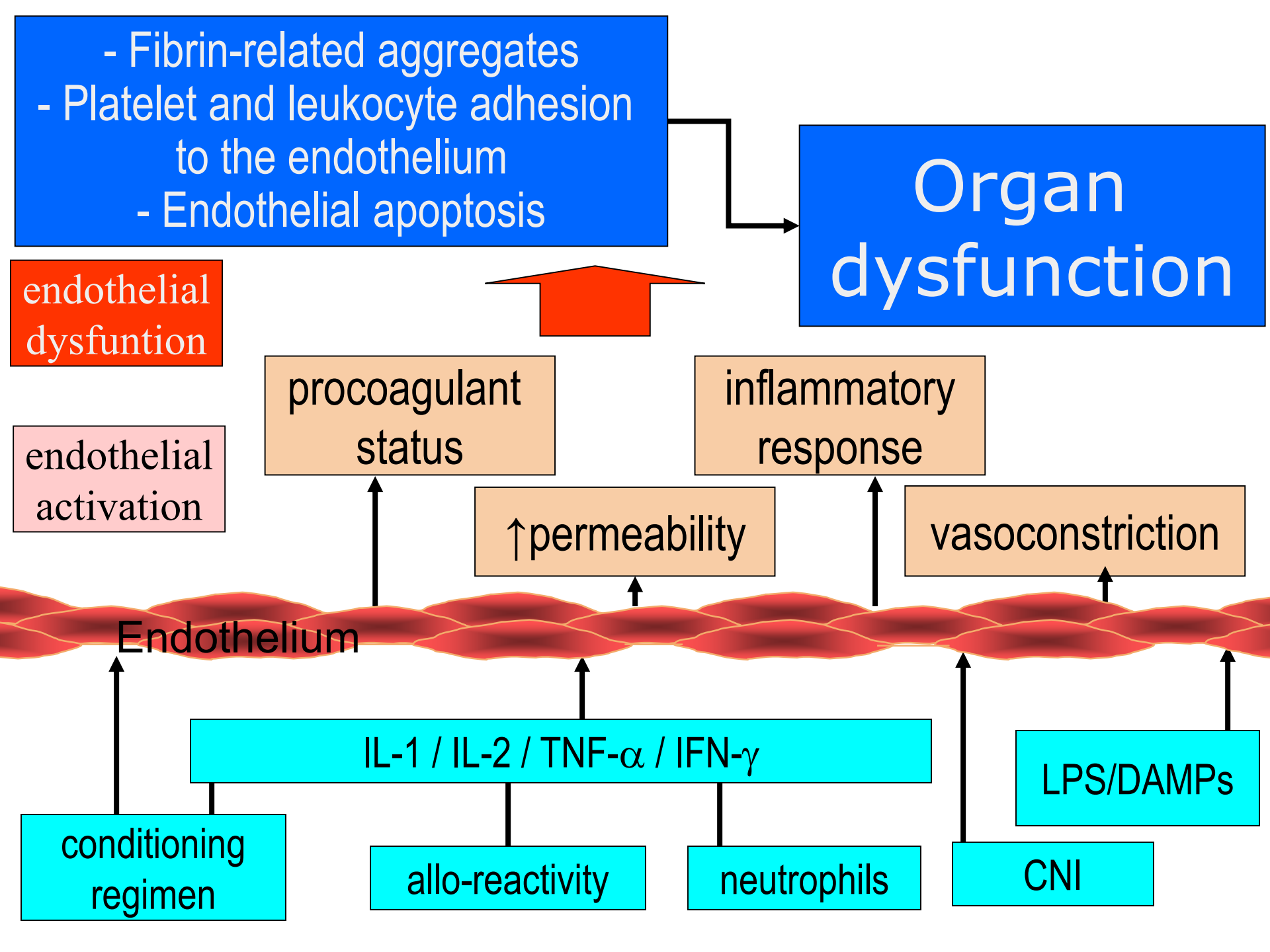
Udine, 21-22 Gennaio 2016

Antonio M. Risitano, M.D., Ph.D.
Federico II University of Naples

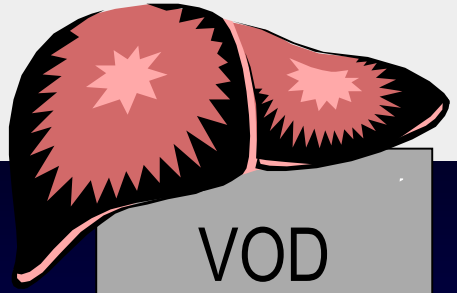
Endothelial complications after HSCT

Time course within different HSCT phases

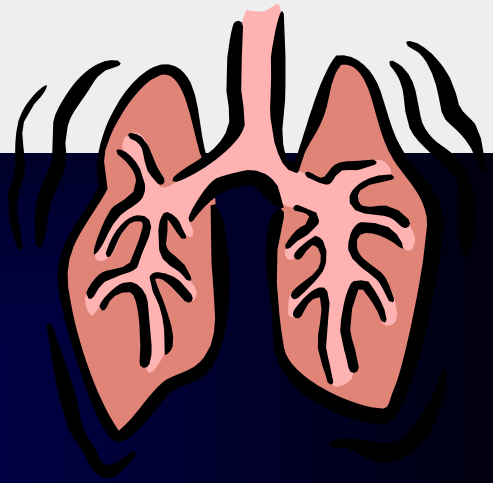



- Fibrin-related aggregates
- Platelet and leukocyte adhesion to the endothelium
- Endothelial apoptosis
Organ dysfunction
endothelial dysfuntion
procoagulant status
inflammatory response
endothelial activation
↑permeability
vasoconstriction
Endothelium
IL-1 / IL-2 / TNF-α / IFN-γ
LPS/DAMPs
conditioning regimen
allo-reactivity
neutrophils
CNI

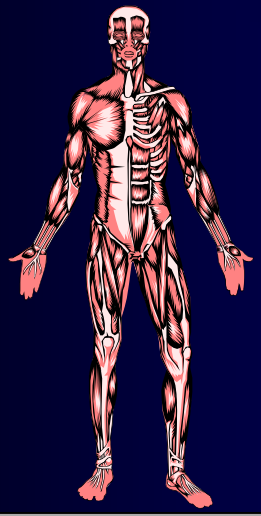
Organ dysfunction



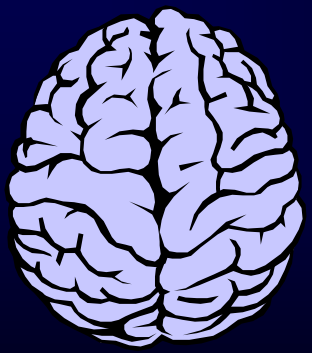
VOD

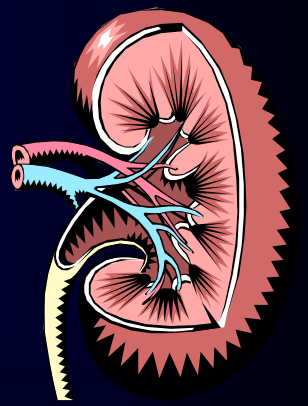


Diffuse alveolar haemorrhage



Thrombotic microangiopathy,
Capillary leak syndrome,
Engraftment syndrome

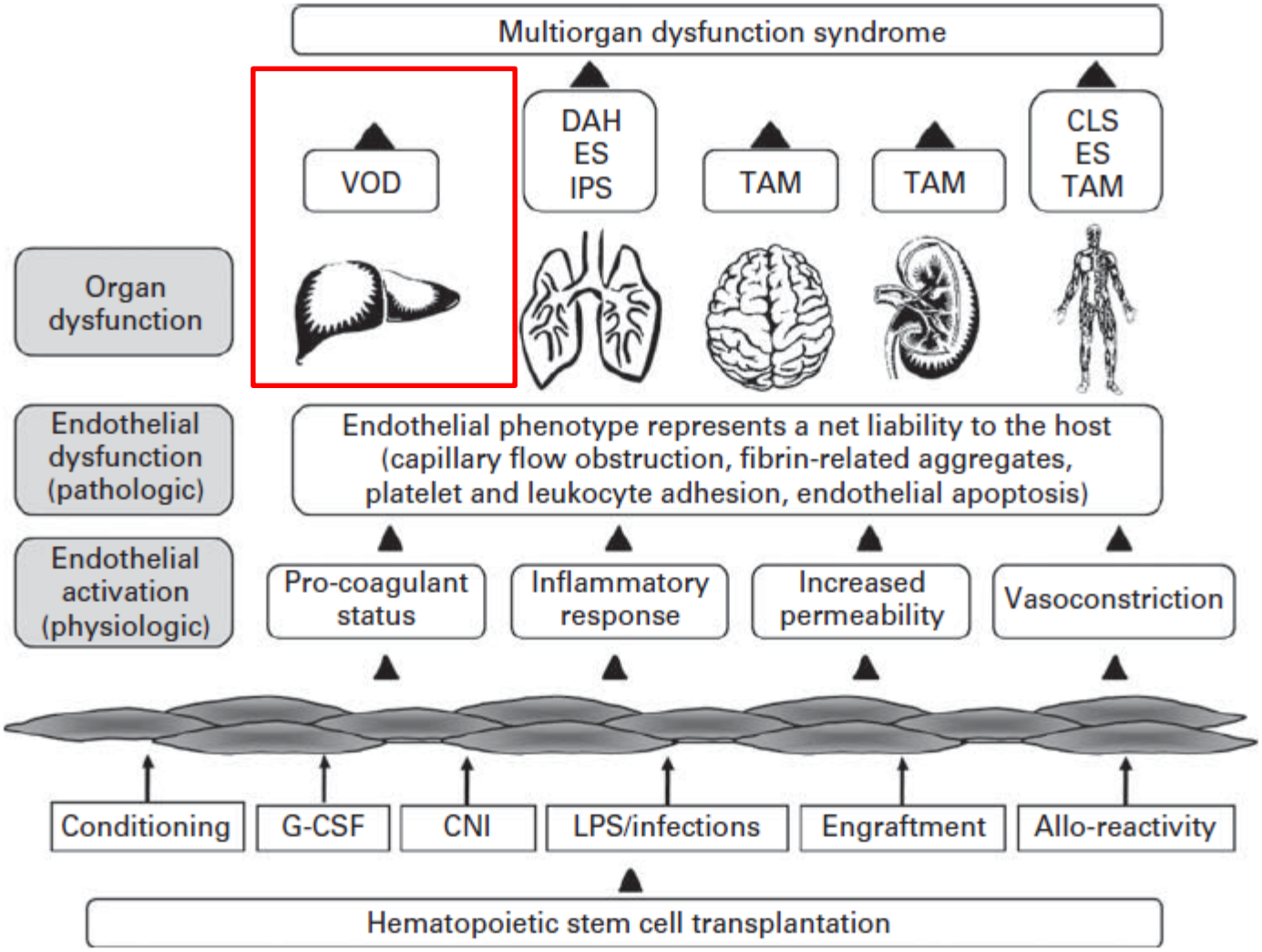




Thrombotic microangiopathy

Endothelial complications after HSCT

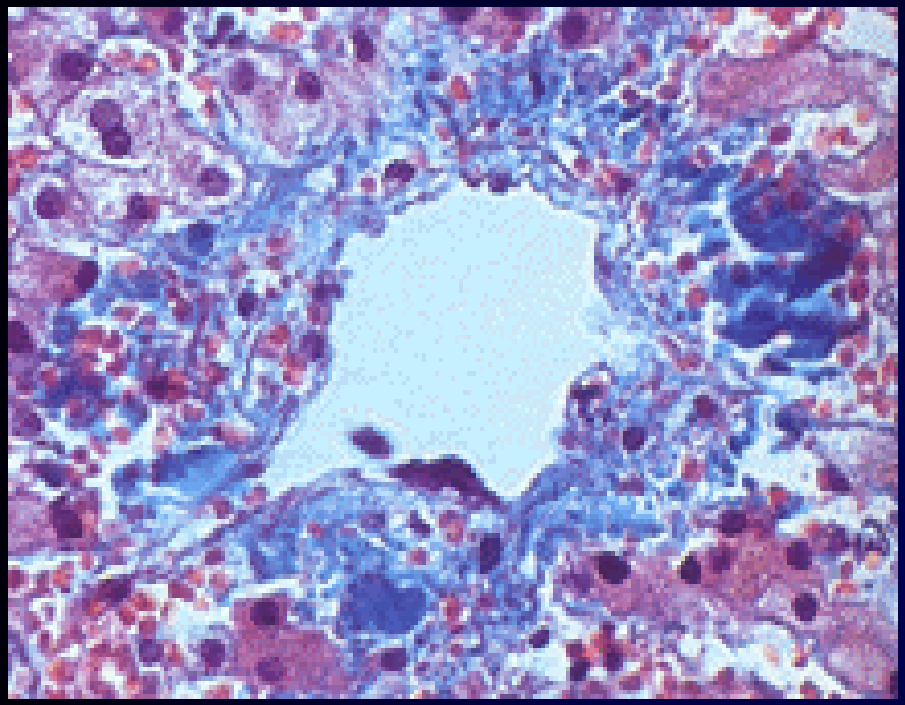
The clinical spectrum

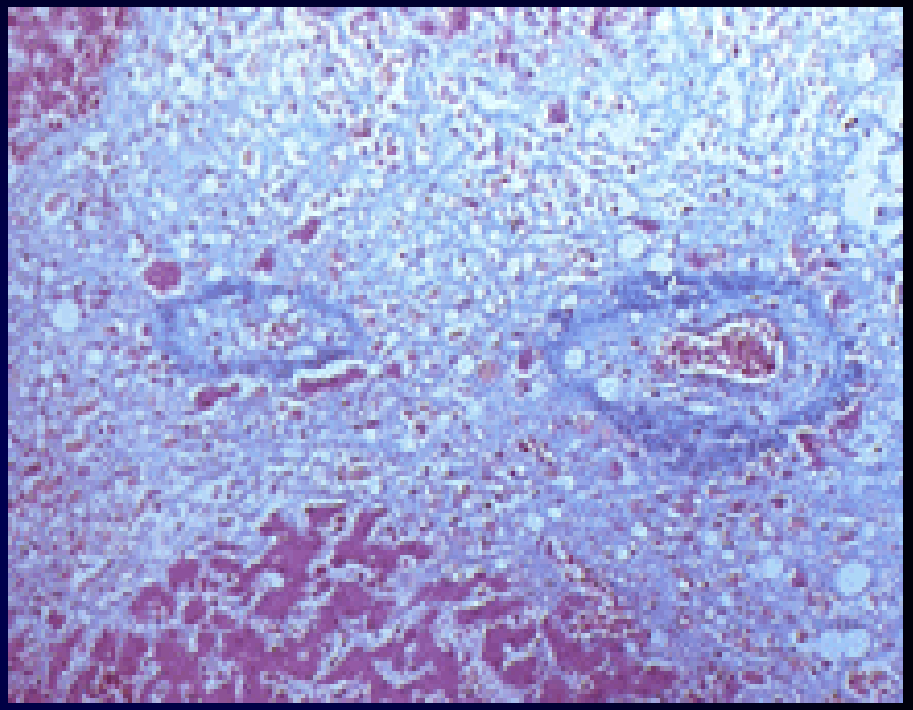


Bone Marrow Transplantation (2011) 46, 1495–1502

Veno-occlusive disease (VOD)

Out knowledge in the '80

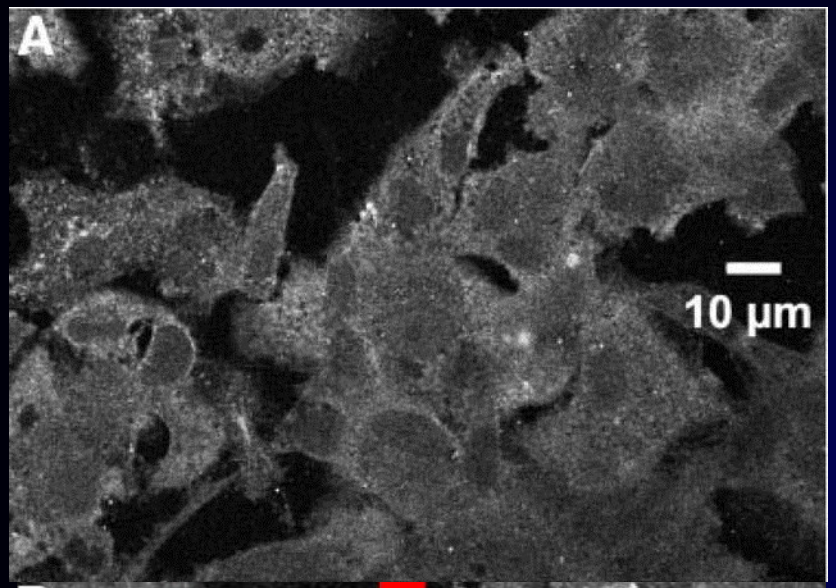


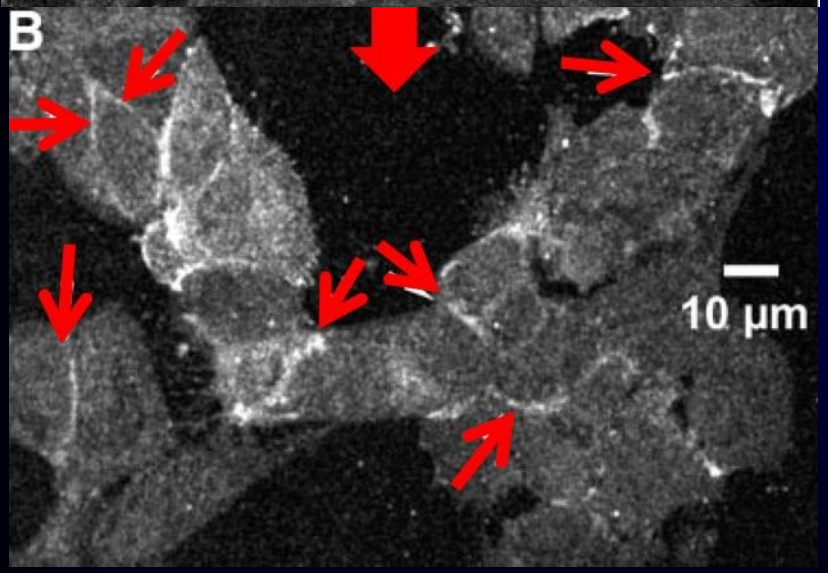


Concentric non-thrombotic narrowing of the lumen of small intrahepatic veins
$\rightarrow$ obstruction of sinusoidal flow

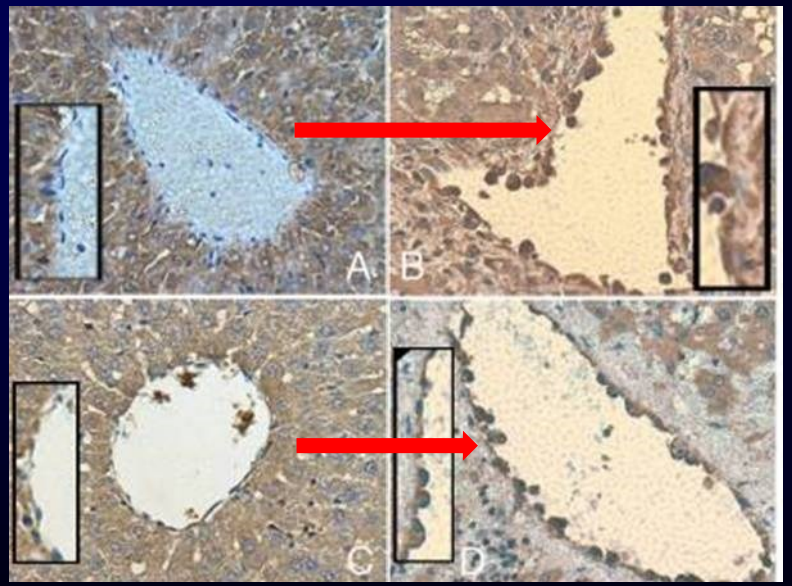
Veno-occlusive disease/sinusoid obstruction syndrome (SOS)

Pathogenic insights from the last decade

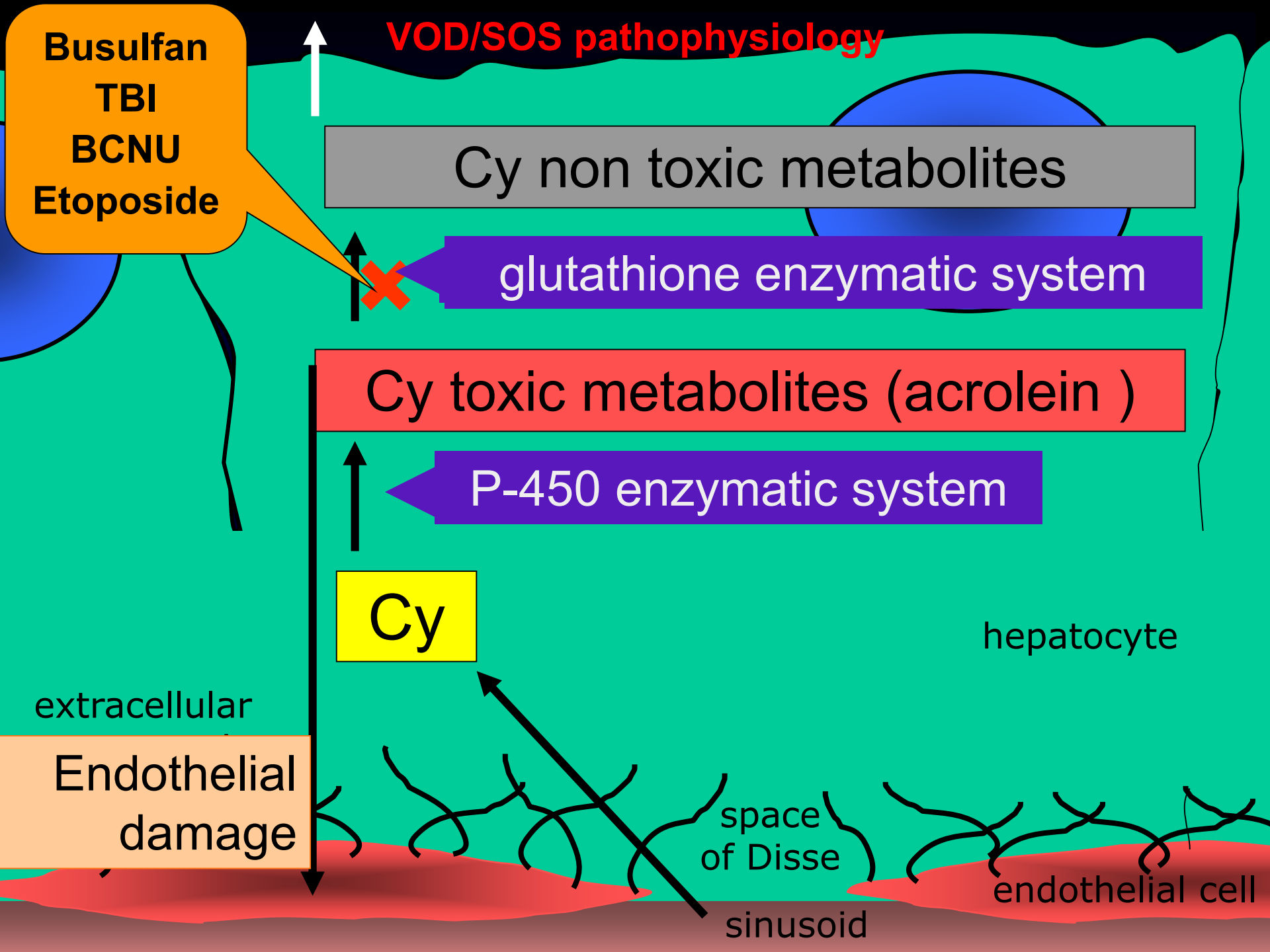




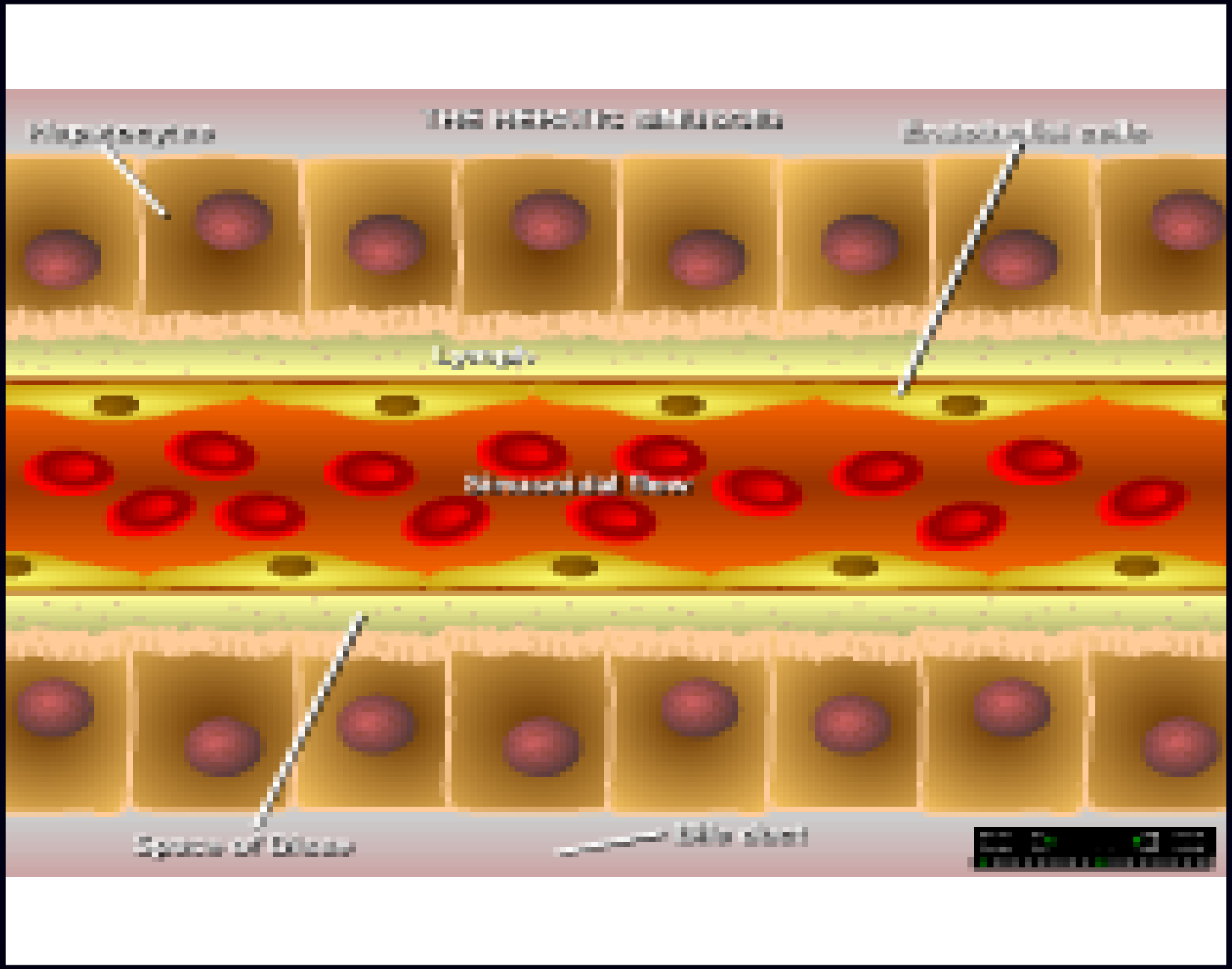
First morphological changes observed in VOD occur in the sinusoidal endothelial cells



DeLeve et al. 2004 and 2009


VOD/SOS pathophysiology
Busulfan
TBI
BCNU
Etoposide
Cy non toxic metabolites
glutathione enzymatic system
Cy toxic metabolites (acrolein)
P-450 enzymatic system
Cy
hepatocyte
extracellular
Endothelial damage
space of Disse
endothelial cell
sinusoid

VOD/SOS pathogenesis

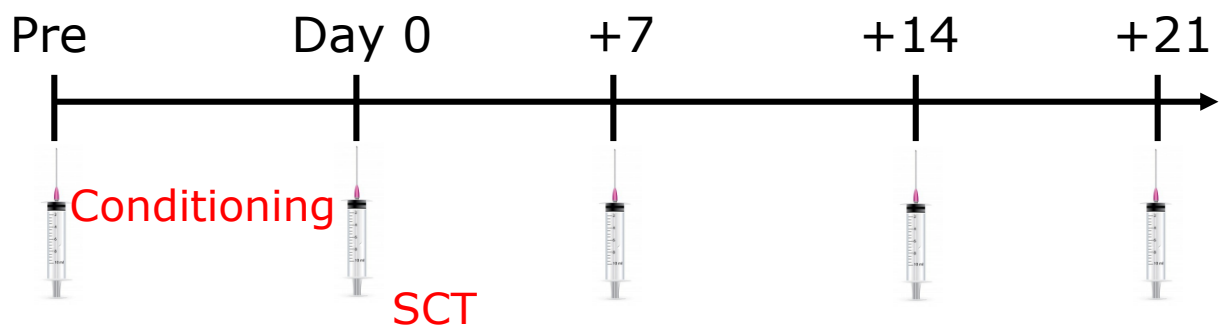


DeLeve et al. 1994 – 2000; Courtesy of Prof. Enric Carreras

Endothelial dysfunction after HSCT

- HSCT performed between 2007–2010
  - Autologous HSCT (BEAM / MLF)
  - Allogeneic HSCT (Cy-TBI / Flu-MLF) (MAC vs RIC)

- Samples (through CVC)



- Soluble markers of endothelial damage
  - Willebrand factor (vWF)
  - ADA
  - S
  - S
  - TNF-alfa receptor I (sTNFR I)

Double peak after allo-HSCT, around d0 and d+21

***ex vivo* studies**

Courtesy of Prof. Enric Carreras

Endothelial changes after HSCT

Phenotype	Auto-HSCT	Allo-HSCT
-Proinflammatory	++	++
-Prothrombotic	±	+++
-Proliferation	++	++
-Proapoptotic	-	++

Veno-occlusive disease (SOS)
Thrombotic microangiopathy

Courtesy of Prof. Enric Carreras

VOD/SOS

Diagnostic criteria

Modified Seattle criteria

- Presentation before Day 20 post-HSCT of two of the following:
  - Bilirubin >2 mg/dL (>34 µmol/L)
  - Hepatomegaly or right upper quadrant pain
  - Weight gain (>2% basal weight)

Baltimore criteria

- Bilirubin level >2 mg/dL (>34 µmol/L) before Day 21 post-HSCT and at least two of the following:
  - Painful hepatomegaly
  - Ascites
  - Weight gain (≥5% basal weight)

Incidence and outcome of VOD

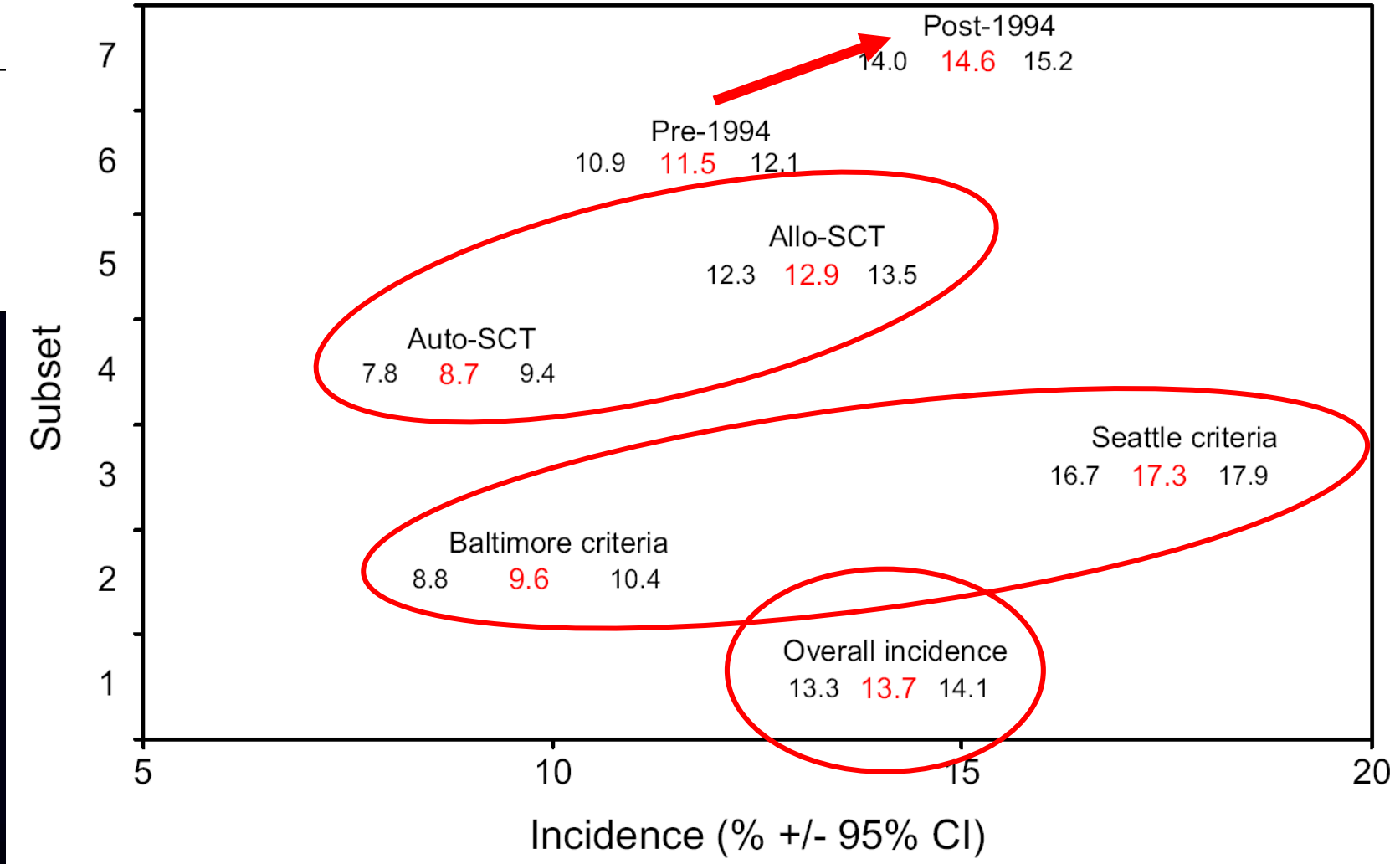
- The incidence of VOD reported in the literature varies greatly
- This wide range is due to variations in:[1–3]
  - Diagnostic criteria
  - Patient- and transplant-related risk factors
  - Sample size
- Two recent studies suggest that the incidence of VOD is 8–14% but can be up to 60% in high-risk patients[1,2]
- VOD is a progressive disease with ranging in severity from a mild, to a severe disease associated with MOF (including renal failure, encephalopathy and coma) and death
- Severe VOD is associated with a high mortality rate of >80%[1]

1. Coppell JA et al. *Biol Blood Marrow Transplant* 2010;16:157–168;
2. Carreras E et al. *Biol Blood Marrow Transplant* 2011 [Epub ahead of print];
3. Helmy A. *Aliment Pharmacol Ther* 2006;23:11–25

VOD/SOS

Incidence

Hepatic Veno-Occlusive Disease following Stem Cell Transplantation: Incidence, Clinical Course,



VOD/SOS

Incidence and outcome; Eric Carreras et al, BBMT 2011

(n=845)	Seattle criteria	Baltimore criteria
VOD cases	117 (CumI 14% ± 2%)	73 (CumI 12% ± 2%)
Diagnostic day	+ 9 (0–44)	+ 8 (0–44)
Mild-Moderate VOD	79 (68%)	38 (52%)
Severe	38 (32%)	35 (48%)
Severe VOD with MOF	26 (22%)	26 (36%)

CumI: cumulative incidence

VOD/SOS

Incidence and outcome; Eric Carreras et al, BBMT 2011

Risk factors for VOD (Baltimore criteria)

Unfavourable	Favourable	Uni variate	Multi variate	Odds Ratio	95% CI
<1997	≥1997	0.014			
CML	Other diagnosis	0.053	0.031	1.96	1–3.6
Unrelated	HLA=sibling	0.001	<0.001	3	1.7–5.4
BM	PBSC	0.025			
Non selected	CD34+ selection	0.017			
Liver disease	Normal liver	0.001	<0.001	3.35	1.7–6.6
↑ ALT	Normal ALT	0.004			
KI <90	KI ≥90	0.02	<0.001	3.18	1.7–5.7

Except for RIC, no relevant changes in risk factors

VOD/SOS

Incidence and outcome; Eric Carreras et al, BBMT 2011

VOD incidence (using Baltimore criteria)

MAC	<1997		≥1997	
	VOD/total	Cuml	VOD/total	Cuml
Whole series	44/385	12%	26/310	8%
P value		0.19		
HLA = sibling	29/335	9%	15/204	7%
P value		0.61		
Unrelated	15/50	33%	11/106	11%
P value		0.002		

Cuml: cumulative incidence

Clearly less VOD among MAC-HSCT from unrelated donor, no differences among those from an HLA identical sibling

Improvement in management in UNR-HSCT? Better donor selection?

VOD/SOS

Incidence and outcome; Eric Carreras et al, BBMT 2011

VOD incidence (using Baltimore criteria)

≥1997	RIC		MAC	
	VOD/total	Cuml	VOD/total	Cuml
Whole series	3/142	2%	26/310	8%
P value		0.01		
HLA = sibling	0/103	0%	15/204	7%
P value		0.005		
Unrelated	3/39	8%	11/106	11%
P value		0.56		

Cuml: cumulative incidence

Clearly less VOD among RIC-HSCT from HLA identical sibling, no differences among those receiving an unrelated donor HSCT

Allo-reactivity counterbalances the beneficial effect of RIC?

VOD/SOS

Incidence and outcome; Eric Carreras et al, BBMT 2011

Evolution and outcome

(n=845)	Seattle criteria		Baltimore criteria	
Severe with MOF	26/117 (22%)		26/73 (36%)	
Died due to VOD	20/117		20/73	
Mortality rate by VOD	Cuml 17% ± 3%		Cuml 27% ± 5%	
– < year 1997	Cuml 22% ± 5%	P=0.06	Cuml 36% ± 7%	P=0.04
– ≥ year 1997	Cuml 9% ± 4%		Cuml 14% ± 6%	

Cuml: cumulative incidence

Since 2000 all patients fulfilling the Baltimore criteria received **defibrotide**

VOD + MOF (n=26)	Died of VOD		Did not die of VOD
Defibrotide NO (n=18)	14 (78%)	P=0.007	4
Defibrotide YES (n=8)	2 (25%)		6

Prophylaxis VOD/SOS

Act on risk factors

OPEN

Bone Marrow Transplantation (2015) **50,** 781–789

www.nature.com/bmt

SPECIAL REPORT

Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives—a position statement from the European Society for Blood and Marrow Transplantation (EBMT)

M Mohty[1,32], F Malard[1,32], M Abecassis[2,32], E Aerts[3,32], AS Alaskar[4,32], M Aljurf[5,32], M Arat[6,32], P Bader[7,32], F Baron[8,32], A Bazarbachi[9,32], D Blaise[10,32], F Ciceri[11,32], S Corbacioglu[12,32], J-H Dalle[13,32], RF Duarte[14,32], T Fukuda[15,32], A Huynh[16,32], T Masszi[17,32], M Michallet[18,32], A Nagler[19,32], M NiChonghaile[20,32], T Pagluica[21,32], C Peters[22,32], FB Petersen[23,32], PG Richardson[24,32], T Ruutu[25,32], BN Savani[26,32], E Wallhult[27,32], I Yakoub-Agha[28,32] and E Carreras[29,30,31,32]

Transplant-related

- Allo-HSCT > auto-HSCT
- Unrelated donor
- HLA-mismatched donor
- Myeloablative conditioning regimen
- BU-based conditioning regimen
- TBI-based conditioning regimen
- Non-T-cell-depleted graft
- Second HSCT

nt- and disease-related

- > younger (in adult patients)
- receiving norethisterone
- score below 90%
- rphism (GSTM1, GSMTT1, heparanase)
- e (beyond second CR or relapse)
- e
- nd resistance to activated protein C

- **Prefer low-toxicity regimens (i.v. Bu, BuFlu; hyper-fract. TBI)**
- **Prevent alloreactivity: donor selection, IST**

Hepatic related risk factors

- Transaminase > 2.5 ULN
- Serum bilirubin > 1.5 ULN
- Cirrhosis
- Hepatic fibrosis
- Active viral hepatitis
- Hepatic irradiation
- Previous use of gemtuzumab ozogamicin
- se of hepatotoxic drugs
- overload

Pedi ific risk factors

- Her cytic lymphohistiocytosis, adrenoleucodystrophy, oste
- High- SCT in neuroblastoma
- Young 2 years of age)
- Low w

- **Avoid hepatotoxic drugs (or modify the dose, i.e. Mylotarg)**
- **Delay HSCT in case of reversible liver disease**

Prophylaxis VOD/SOS

Pharmacological prophylaxis

Drug	Efficacy
Unfractionated heparin and low molecular weight heparin	Meta-analisys [1] → inconclusive results
Prostaglandine E1	No efficacy, high toxicity[2]
N-acetilcisteina	Few evidences
Antitrombine III	No efficacy[3]

1. Imran H et al. Bone Marrow Transplant 2006;37:677-686. **2.** Bearman SI et al Brit J Haematol 1993;84:724-730. **3**. Haussmann U et al. Haematologica 2006;91:795-800.**4**

Biology of Blood and Marrow Transplantation 13:206-217 (2007)

1083-8791/07/1302-0001$32.00/0
doi:10.1016/j.bbmt.2006.09.012

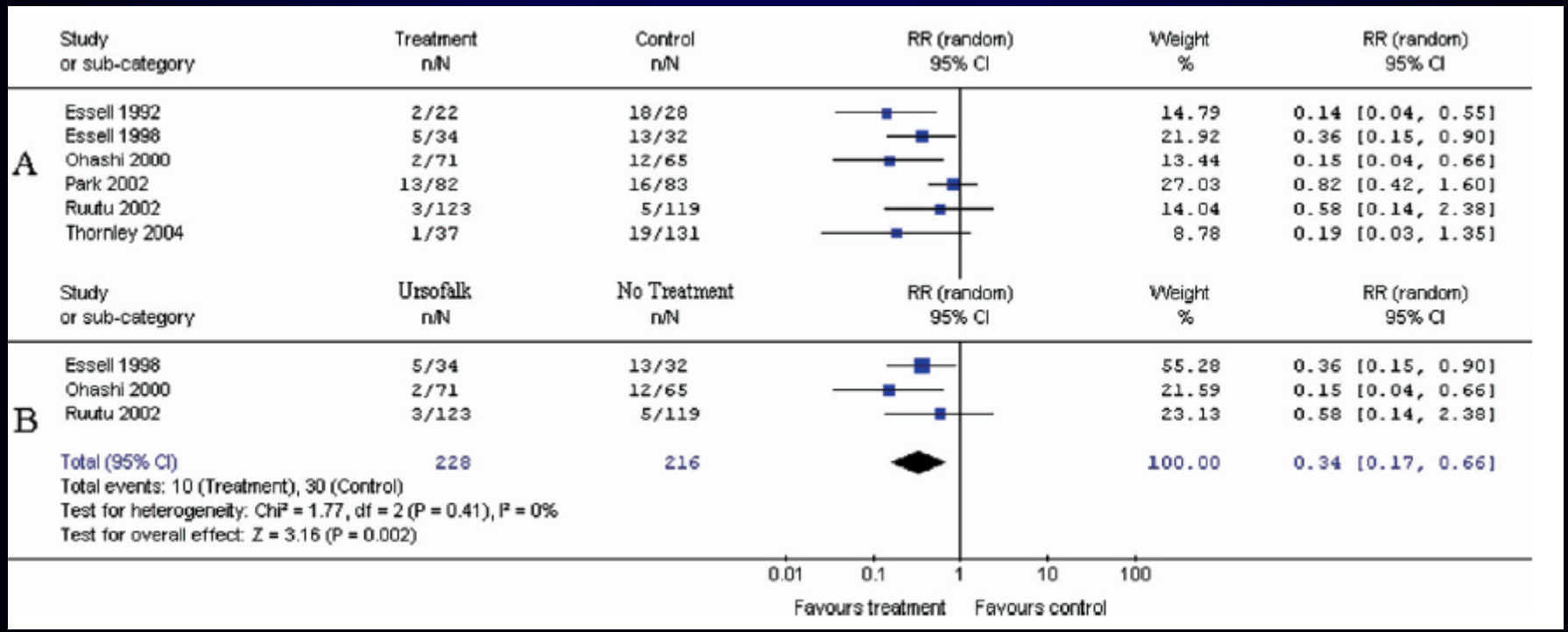
ASBMT
American Society for Blood and Marrow Transplantation

Systematic Review of Controlled Clinical Trials on the Use of Ursodeoxycholic Acid for the Prevention of Hepatic Veno-occlusive Disease in Hematopoietic Stem Cell Transplantation

Jason Tay,[1,4] Alan Tinmouth,[2,4,6] Dean Fergusson,[3,4] Lothar Huebsch,[1,2] David S. Allan[1,2,5,6]

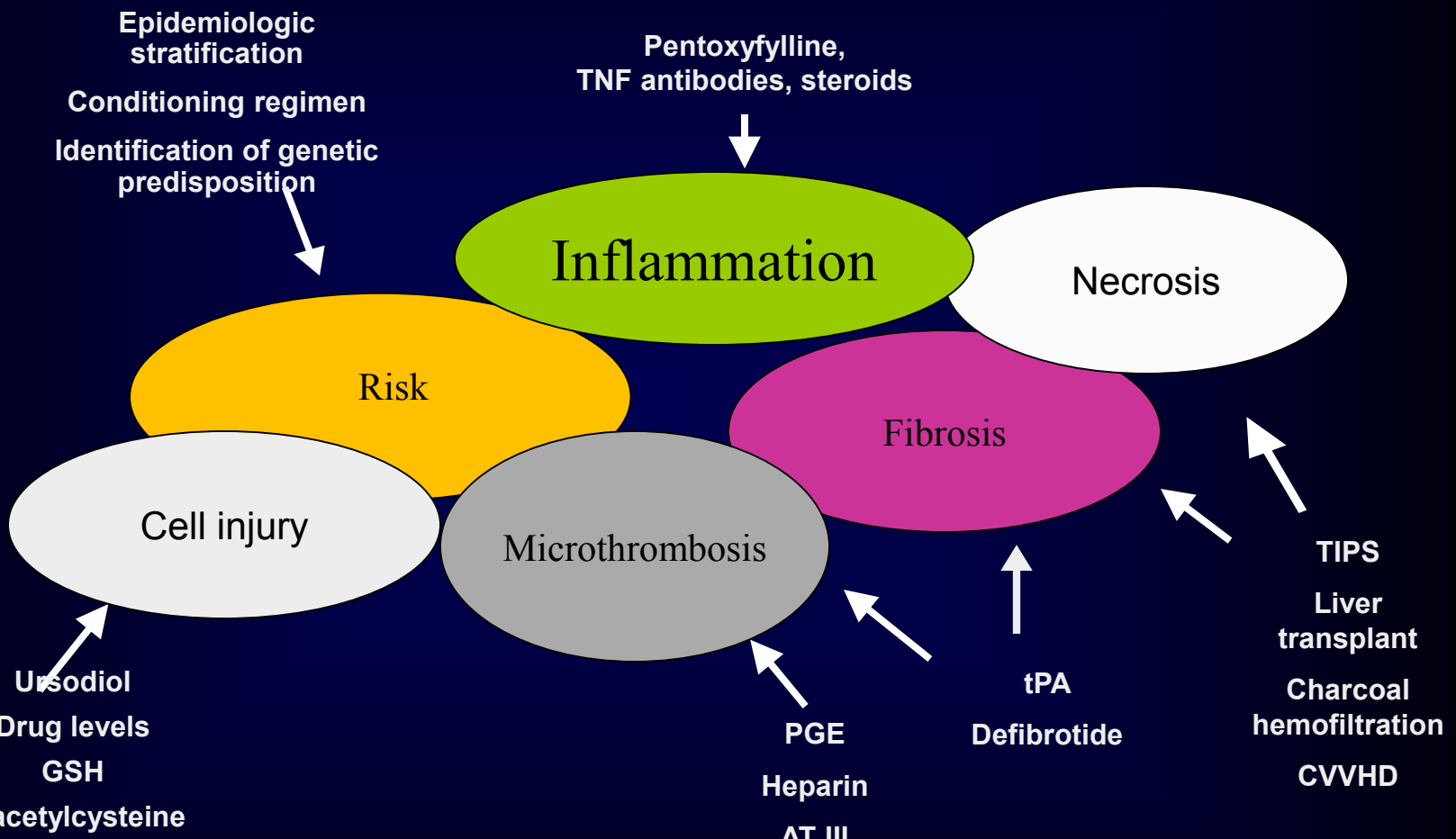
Ursodeoxycholic acid reduce the risk of VOD/SOS (RR 0,34; CI 0,17-0,66) in a systematic review of 6 studies (4 randomized)

Figure 2. Forest plots of (A) hepatic veno-occlusive disease (primary outcome) in all studies and (B) pooled estimate of hepatic veno-occlusive disease from randomized trials. CI indicates confidence interval; RR, relative risk.



Treatment of VOD/SOS

Potential points of intervention



TNF, tumor necrosis factor; GSH, glutathione;
PGE, prostaglandin E; AT III, antithrombin III; APC, activated protein C;
LMWH, low molecular weight heparins; tPA, tissue plasminogen activator;
TIPS, transjugular intrahepatic portosystemic shunt;
CVVHD, continuous veno-venous haemodialysis

Biological properties of defibrotide

- The major effects of defibrotide are:
  - **Reducing inflammation**[1] by decreasing local cytokine release[1]
  - **Inhibiting thrombosis** by decreasing levels of tissue thromboplastin and increasing TFPI[1]
  - **Inducing fibrinolysis** by increasing levels of tPA and by reducing PAI-1 levels, which have been demonstrated to play a key role in VOD[1–4]
  - **Blocking TF expression**, the most important activator of the coagulation cascade which may help reduce microvascular fibrin deposition[1,3,4]
  - **Modulating platelet activity** by increasing levels of endogenous prostaglandins (PGI-2 and E-2)[1–3]

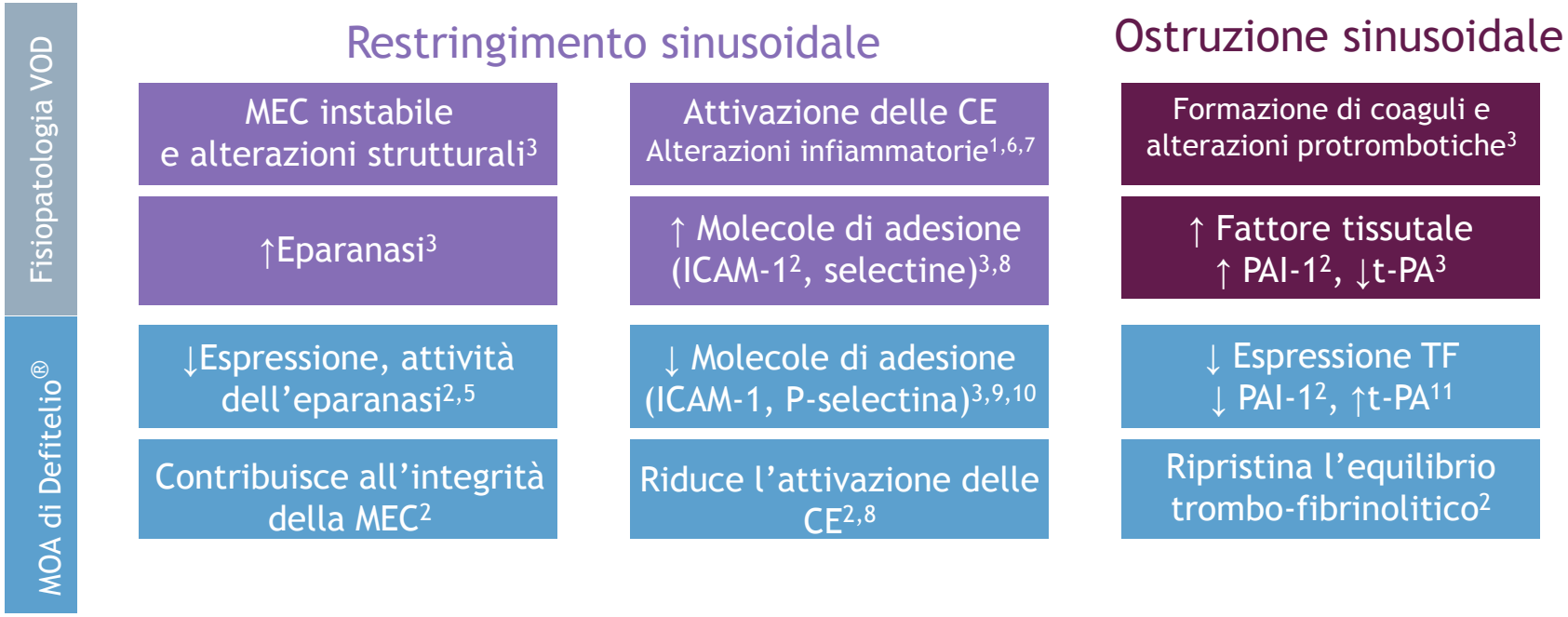
Defibrotide protects and stabilises endothelium without enhancing systemic bleeding[1]

TFPI, tissue factor pathway inhibitor;
PAI-1, plasminogen activator inhibitor 1; TF, tissue factor

1. Morabito F et al. *Expert Opin Biol Ther* 2009;9:763–772
2. Coccheri S & Biagi G. *Cardiovasc Drug Rev* 1991;9:172–196;
3. Palmer KJ & Goa KL. *Drugs* 1993;45:259–294;
4. Falanga A et al. *Leukemia* 2003;17:1636–1642

Defitelio® ha come bersaglio la cellula endoteliale e svolge azioni multifattoriali per trattare la sVOD[1]

> Defitelio® esercita effetti mediati dalla cellula endoteliale sulle maggiori cascate di eventi nella sVOD[2-4]



MEC, matrice extracellulare; CE, cellula endoteliale; ICAM-1, molecola di adesione intercellulare 1; P-selectina, selectina piastrinica; PAI-1, inibitore dell'attivatore del plasminogeno-1; t-Pa, attivatore tissutale del plasminogeno; TF, fattore tissutale; MOA, meccanismo d'azione (mode of action)

1. Pescador R, et al. Cardiovasc Drug Rev 2000; 18(4): 304–311. 2. Defitelio® Summary of Product Characteristics March 2015. 3. Richardson PG, et al. Biol Blood Marrow Transplant 2013; 19: S88–90. 4. DeLeve LD, et al. Vascular Liver Disease and the Liver Sinusoidal Endothelial Cell. Vascular Liver Disease: Mechanisms and Management. New York: Springer, 2011: 25–40. 5. Mitsiades CS, et al. Clin Cancer Res 2009; 15: 1210–1221. 6. Carreras E and Diaz-Ricart M. Bone Marrow Transplant 2011; 46: 1495–1502. 7. Félétou M. Chapter 2: Multiple Functions of the Endothelial Cells. The Endothelium —Focus on Endothelium-Derived Vasoactive Mediators. San Rafael (CA): Morgan & Claypool Life Sciences, 2011. 8. Pescador R, et al. Vascular Pharmacology 2013; 59(1): 1–10. 9. Palomo M, et al. Biol Blood Marrow Transplant 2011; 17: 497–506. 10. Scalia R, et al. Meth Find Exp Clin Pharmacol 1996; 18: 669–676. 11. Falanga A. Leukemia. 2003; 17: 1636–1642.

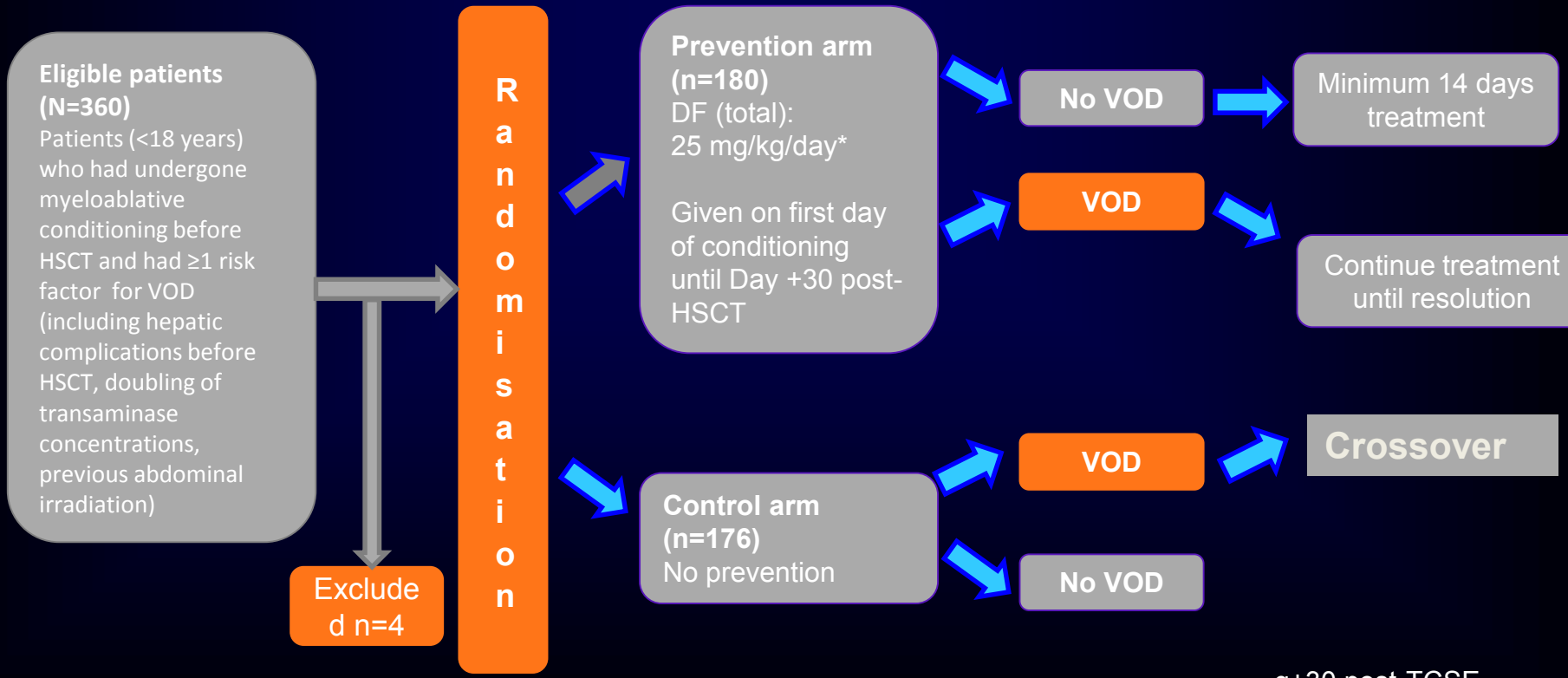
Prophylaxis VOD/SOS

Defibrotide

Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial

Lancet 2012; 379: 1301–09

Selim Corbacioglu, Simone Cesaro, Maura Faraci, Dominique Valteau-Couanet, Bernd Gruhn, Attilio Rovelli, Jaap J Boelens, Annette Hewitt, Johanna Schrum, Ansgar S Schulz, Ingo Müller, Jerry Stein, Robert Wynn, Johann Greil, Karl-Walter Sykora, Susanne Matthes-Martin, Monika Führer, Anne O'Meara, Jacek Toporski, Petr Sedlacek, Paul G Schlegel, Karoline Ehlert, Anders Fasth, Jacek Winiarski, Johan Arvidson, Christine Mauz-Körholz, Hulya Ozsahin, Andre Schrauder, Peter Bader, Joseph Massaro, Ralph D'Agostino, Margaret Hoyle, Massimo Iacobelli, Klaus-Michael Debatin, Christina Peters*, Giorgio Dini*



g+30 post-TCSE

Prophylaxis VOD/SOS

Defibrotide

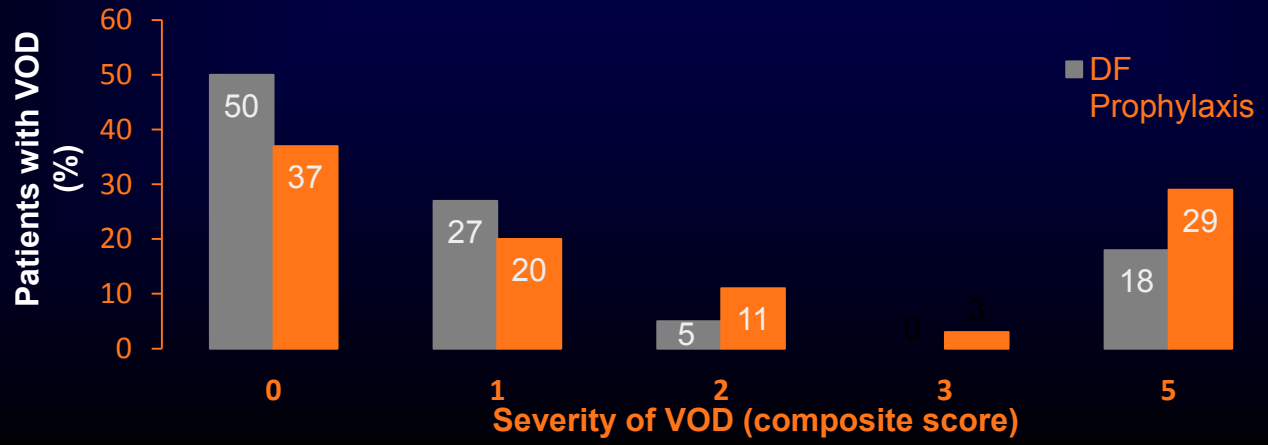
Corbacioglu, lancet 2012

Primary end-point, Incidence of VOD

Intent-To-Treat Analysis: all randomised patients

	Defibrotide Prophylaxis	Control	P value
Competing Risk:	12% (22/180)	20% (35/176)	**0.0488**[(b)]
CICR (95% CI) [(a)]	0.13 (0.08,0.19)	0.20 (0.15,0.27)	

- Severity of VOD, as assessed by composite severity score based on MOF and death up to 100 days post-HSCT, was lower than controls (Wilcoxon test p=0.0340, based on ITT population at Day + 100)



Prophylaxis VOD/SOS

Defibrotide

Corbacioglu, lancet 2012

Lower incidence of VOD-associated renal dysfunction and aGVHD

Event	Defibrotide (n=180) n (%)	Control (n=176) n (%)
Respiratory failure	11 (6)	15 (9)
Renal failure	**2 (1)**	**10 (6)***
Encephalopathy	1 (1)	3 (2)
Mortality	4 (2)	10 (6)
No organ failure or mortality	169 (94)	159 (90)

Allogeneic SCT	DF Prophylaxis (n=122)	Control (n=117)	p-value
Acute GvHD by Day+100	47% (57)	65% (76)	**0.005***
- GvHD Grade 1	25% (30)	28% (33)	**0.003****
- GvHD Grade 2	15% (18)	26% (30)	
- GvHD Grade 3	4% (5)	8% (9)	
- GvHD Grade 4	3% (4)	3% (4)	

Treatment of VOD/SOS

Who, when and how?

The first step in the treatment of SOS/VOD is symptomatic

- **Maintenance of adequate fluid and electrolyte balance**
- **Avoid hepatotoxic and nephrotoxic drugs**
- **Careful use of diuretics (furosemide or spironolactone)**
- **In the event of progression of symptoms support strategies: analgesia, paracentesis, thoracentesis, oxygen therapy**
- **Possible hemodialysis / hemofiltration**

Carreras E. How I manage sinusoidal obstruction syndrome after haematopoietic cell transplantation. Br J Haematol 2014; 168: 481–491

Treatment of VOD/SOS

Tissue plasminogen activator

Author	No of patients	Dose (mg/d)	Duration (d)	Heparin (yes/no)	No of responses	Life-threatening hemorrhage
Baglin et al. (1990)	1	50	4	No	1	0
Bearman et al. (1997)	**42**	**5.4–120**	**2–4**	**Yes**	**12**	**10**
LaPorte et al. (1992)	1	50	4	No	1	0
Rosti et al. (1992)	1	50	4	No	1	0
Ringden et al. (1992)	1	50	4	No	0	1
Leahey et al. (1996)	9	5–10	2–4	Yes	5	0
Feldman et al. (1995)	3	15	4	No	3	0
Goldberg et al. (1996)	1	20	4	Yes	1	0
Higashigawa et al. (1995)	1	2–3	4	Yes[1]	1	0
Hagglund et al. (1995)	**10**	**3–50**	**3–8**	**Yes[2]**	**4**	**4**
Lee et al. (1996)	3	10–20	7–14	Yes	3	0
Yu et al. (1994)	3	0.25–0.5[3]	4	No	2	0
Schriber et al. (1999)	**37**	**30-–40**	**1–21**	**Yes**	**10[4] (9)[4]**	**13**
Kulkarni et al. (1999)	**17**	**10**	**1–12**	**Yes**	**6**	**0**

[1]patient also received PGE; [2]three patients received heparin, seven patients did not; [3]dose reported as mg/kg; [4]in patients who met established criteria for VOD

Treatment of VOD/SOS

Defibrotide

Table 2. Main studies on defibrotide in SOS/VOD

	Reference; Phase; Number of patients	*Condition*	*Design*	*Key points*	*Others results*
	Richardson *et al.*[67] Retrospective CUP $N=19$	Adult and pediatric Severe SOS/VOD post HSCT	Compassionate use; DF: 5–60 mg/kg per day (intra-pt dose escalation, until response/toxicity)	CR: 42% Minimal toxicity at doses tested	Day +100 survival: 32%
	Richardson *et al.*[68] Phase I/II $N=88$	Adult and pediatric Severe SOS/VOD post HSCT	Emergency use; DF: 5–60 mg/kg per day (intra-pt dose escalation, until response/toxicity)	CR: 36% Active dose range 25–40 mg/kg per day	Day +100 survival: 35% No serious AEs attributed to DF
2	Richardson *et al.*[57] Phase II $N=149$	Adult and pediatric Severe SOS/VOD post HSCT	Randomized, dose-finding; Arm A: DF 25 mg/kg per day Arm B: DF 40 mg/kg per day For 14 days or more.	Day +100 CR: 46% Effective dose 25 mg/kg per day	Day +100 survival: 42% Overall SAE incidence: 8% (greater at 40 vs 25 mg/kg per day)
1	Richardson *et al.*[58] Phase III $N=102$	Adult and pediatric Severe SOS/VOD post HSCT	Non-randomized, comparison with historical control; DF: 6.25 mg/kg i.v. q6h (25 mg/kg per day) for 21 days or more.	Day +100 CR DF 24% HC 9% ($P=0.0131$)	Day +100 mortality: DF 62%; HC 75% ($P=0.0341$) Hemorrhagic AEs: DF 65%; HC 69%
3	Richardson *et al.*[59] Prospective T-IND $N=470$	Adult and pediatric SOS/VOD non-HSCT ($N=45$) SOS/VOD post HSCT ($N=141$) Severe SOS/VOD post HSCT ($N=284$)	Investigational new drug protocol; DF: 6.25 mg/kg i.v. q6h (25 mg/kg per day) for 21 days or more.	Day +100 CR Non-HSCT 40% SOS/VOD post HSCT 47% Severe SOS/VOD post HSCT 29%	Day +100 survival: Non-HSCT 62% SOS/VOD post HSCT 69% Severe SOS/VOD post HSCT 48% Overall hemorrhagic AEs: 18%

57 Richardson P, BBMT 2010
58 Richardson P, ASH 2009; 114: 654.
59 Richardson P, ASH 2013; 122: 700–700
67 Richardson P, Blood 1998
68 Richardson P, Blood 2002

Mohty M, BMT 2015

Defibrotide for the treatment of VOD/SOS

Clinical trials

	Protocol 2005-01[1]	Protocol 2006-05[2]	Protocol 99-118 [3]
Study design	Pivotal, historically controlled (severe VOD)	Treatment IND	Randomized, open-label dose-finding study
Treatment schedule	TG: DF 25 mg/kg/day HC: treated as per institutional standard	DF 25 mg/kg/day	Arm A: DF 25 mg/kg/day Arm B: DF 40 mg/kg/day
Number of patients	TG: 102 HC: 32	104 (405)	Total: 149 Arm A: 75 Arm B: 74
Sites	35 centres in USA, Canada, Israel	36 (72) centres in USA	6 centres in USA
Status	Complete	Interim analysis	Complete

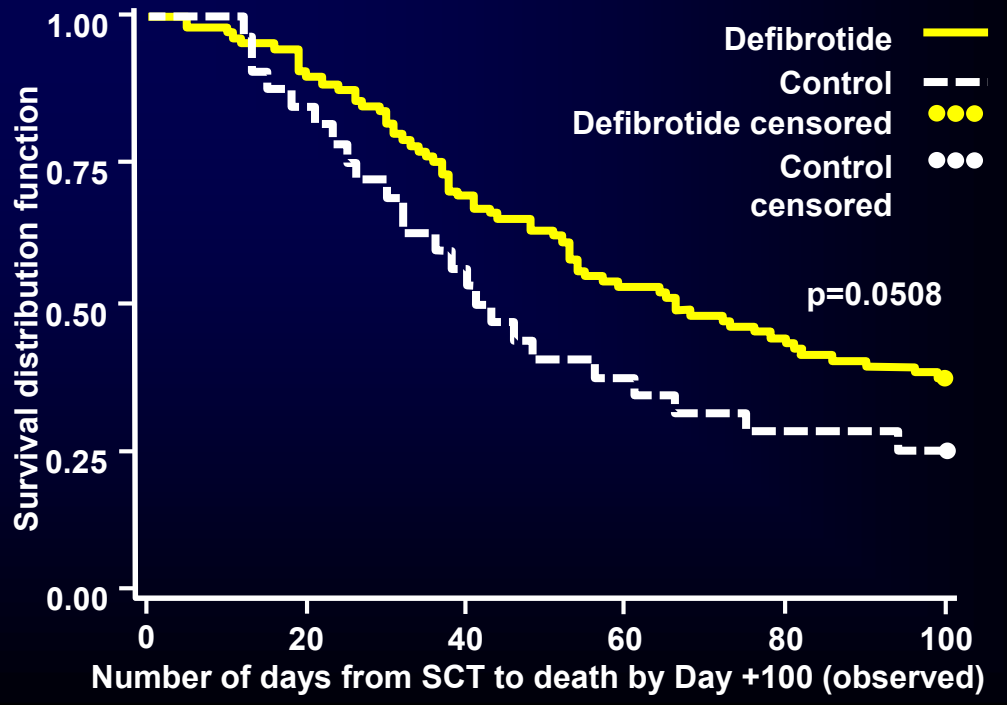
TG, treatment group; HC, historical control; DF, defibrotide

1. Richardson et al *Blood (ASH Annual Meeting Abstracts)* 2009;114:654;
2. Richardson P et al. *Blood (ASH Annual Meeting Abstracts)* 2010;116:906;
3. Richardson PG et al. *Biol Blood Marrow Transplant* 2010;16:1005–1017

1 Richardson P, et al.
Results of a Phase 3 study utilizing a historical control. Defibrotide (DF) in the treatment of severe hepatic veno-occlusive disease (VOD) with multi-organ failure (MOF) following stem cell transplantation (SCT). ASH Annual Meeting Abstracts 2009; 114: 654.

	DF arm (102 pts)	Historical control group (32 pts)	p
CR	24%	9%	0.013
+100 OS	38%	25%	0.034
Hemorragic adverse events	65%	69%	Ns

Given the life-threatening nature of SOS/VOD a trial randomizing patients to placebo or supportive care was rejected



2

ASBMT
American Society for Blood and Marrow Transplantation

Defibrotide for the Treatment of Severe Hepatic Veno-Occlusive Disease and Multiorgan Failure after Stem Cell Transplantation: A Multicenter, Randomized, Dose-Finding Trial

Paul G. Richardson,[1] Robert J. Soiffer,[1] Joseph H. Antin,[1] Hajime Uno,[2] Zhezhen Jin,[3] Joanne Kurtzberg,[4] Paul L. Martin,[4] Gideon Steinbach,[5] Karen F. Murray,[6] Georgia B. Vogelsang,[7] Allen R. Chen,[7] Amrita Krishnan,[8] Nancy A. Kernan,[9] David E. Avigan,[1] Thomas R. Spitzer,[1] Howard M. Shulman,[5] Donald N. Di Salvo,[10] Carolyn Revta,[1] Diane Warren,[1] Parisa Momtaz,[1] Gary Bradwin,[11] L. J. Wei,[12] Massimo Iacobelli,[13] George B. McDonald,[5] Eva C. Guinan[14]

Biol Blood Marrow Transplant 16: 1005-1017 (2010)

- ✓ 25 mg/kg per day (n = 75) vs 40 mg/kg per day, (n = 74).
- ✓ CR rate (49 vs 43%; P = 0.613)
- ✓ day +100 OS (44 vs 39%; P = 0.619).

The effect of dose

Dose (mg/kg/day)	Complete Response (D +100)	Confidence Interval (LL, UL)
10	9.7% (3/31)	0.0%, 20.1%
25	28.8% (23/80)	18.8%, 38.7%
40	24.5% (12/49)	12.4%, 36.5%
60	36.4% (8/22)	16.3%, 56.5%

Pooled data from all studies

Prof. D. Niederwieser (EBMT 2011)

3 Richardson PG, et al.

*Results of the large **prospective study** on the use of defibrotide (DF) in the treatment of hepatic veno-occlusive disease (VOD) in hematopoietic stem cell transplant(HSCT). Early intervention improves outcome - updated results of a treatment IND (T-IND) expanded access protocol.*

ASH Annual Meeting Abstracts 2013; 122: 700–700.

	CR Day +100	Survival Day +100
DF		
DF		
Pediatric (n=32)	38% (12/32)	38% (12/32)
Adult (n=52)	25% (13/52)	25% (13/52)
Ventilator-/ dialysis-dependent (n=36)	22% (8/36)	25% (9/36)

These studies led to the approval in 2014 of DF for treatment of severe SOS/VOD after HSCT in European countries by the European Medicines Agency (EMA).

	Severe VOD 248 pts	Non severe VOD 141 pts	adult	children
CR	47 %	47%	27%*	41%*
+100 OS	48%	69%	49%*	60%*
* p< 0.05				

Pooled data from all studies

Treatment of VOD/SOS

Defibrotide

The effect of timely treatment

Delay in the initiation of Defibrotide treatment > 2 days from VOD/sVOD diagnosis results in higher mortality at Day 100 post-SCT

Richardson, ASH 2009

	Time from VOD diagnosis to DF Administration (N=103)*		
	[illegible]	[illegible]	[illegible]

Mandatory: timely initiation of treatment when diagnostic criteria are met

Delay in the initiation of Defibrotide treatment > 3 days from VOD diagnosis results in higher mortality at Day 100 post-SCT

Niederwieser, EBMT 2011

Pooled data from all studies

	Time from VOD diagnosis to DF Administration (N=572)		
	≤ 3 Days	> 3 Days	P-value
Survival at Day+100	**242/401 (60%)**	**84/171 (49%)**	**0.048**

p values calculated based on the Chi square test.

* Data for 1 pt was missing at the time of analysis

Defibrotide for the treatment of VOD/SOS

Adverse events

	All patients treated 25 mg/kg/day n=419	Patients at 25 mg/kg/day eligible for 2005-01 n=231	Patients treated at 40 mg/kg/day n=75	HC n=32
All adverse events	363 (87%)	196 (85%)	74 (99%)	32 (100%)
All hemorrhagic events	169 (40%)	109 (47%)	43 (57%)	23 (72%)

- Safety database of 1986 patients with VOD treated with DF showed that the frequency of treatment-related SAEs was low
- Most frequent include gastrointestinal hemorrhage (2.57%), pulmonary hemorrhage (2.32%), hypotension (1.56%), coagulopathy (1.36%) and epistaxis (1.01%)
- Other events were reported with less than 1% frequency

Prof. D. Niederwieser (EBMT 2011)

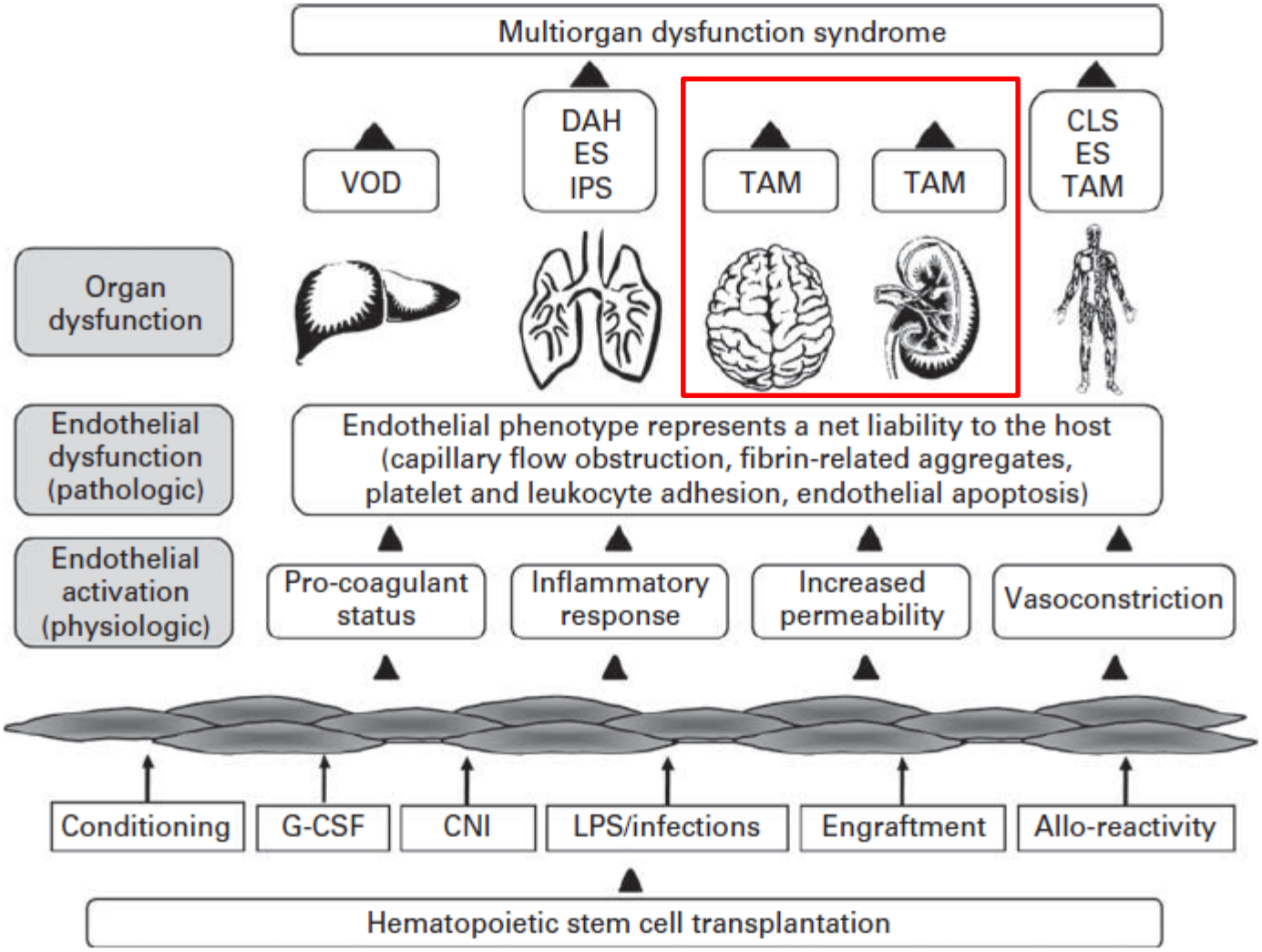
Defibrotide for the treatment of VOD/SOS

Summary

- ✓ Defibrotide is the first and only therapy approved in the European Union for the treatment of severe VOD in HSCT
- ✓ Defibrotide is recommended for the treatment of severe VOD by the EBMT and the latest BCSH/BSBMT guidelines
- ✓ Defibrotide is indicated in adults, adolescents and children and infants >1 month of age
- ✓ The recommended dose for administration is 6.25 mg/kg body weight every 6 hours (25 mg/kg/day), and it should be administered for a minimum of 21 days
- ✓ Standardized (early) diagnostic criteria, severity stratification and response criteria are essential to compare data
- ✓ Confirmatory randomized trials would be useful, but likely hard to be performed

Endothelial complications after HSCT

The clinical spectrum



Bone Marrow Transplantation (2011) 46, 1495–1502

Complement-mediated hemolytic anemias

A tentative classification

Primary: impairment of physiologic complement regulation

- ✓ Systemic impairment: atypical hemolytic-uremic syndrome (aHUS)
- ✓ Local (blood cell surface) impairment: paroxysmal nocturnal hemoglobinuria

Secondary: hyperactivation of the complement cascade

- ✓ Antibody-mediated hemolytic anemias
  - Cold agglutinine disease
  - Cold paroxysmal hemoglobinuria (Donath-Landsteiner Ab)
  - Other AIHA
- ✓ Thrombotic microangiopathies
  - Typical (sporadic) hemolytic-uremic syndrome (HUS)
  - Thrombotic thrombocytopenic purpura (TTP)
  - Transplant-associated microangiopathies (TAM)

Diagnostic criteria for hematopoietic stem cell transplant-associated microangiopathy: results of a consensus process by an International Working Group

Tapani Ruutu, Giovanni Barosi, Richard J. Benjamin, Richard E. Clark, James N. Geo
Alois Gratwohl, Ernst Holler, Massimo Iacobelli, Karim Kentouche, Bernhard Lämml
Joel L. Moake, Paul Richardson, Gerard Socié, Zella Zeigler, Dietger Niederwieser,
Tiziano Barbui *on an initiative of the European Group for Blood and Marrow Transpl*
the European LeukemiaNet

Table 3. The definition of transplant-associated microangiopathy (TAM) by the International Working Group.

All of the following present

- Increased percentage (>4%) of schistocytes in peripheral blood
- *De novo*, prolonged or progressive thrombocytopenia (platelet count less than $50x10^9$/L or a 50% or greater decrease from previous counts)
- Sudden and persistent increase in LDH
- Decrease in hemoglobin concentration or increased red blood cell transfusion requirement
- Decrease in serum haptoglobin concentration

Table 1. Ranking of candidate criteria.

N.	Diagnostic criterion	Sum of ranks
1	RBC fragmentation	323
2	*De novo*, prolonged or progressive thrombocytopenia	301
3	Sudden and persistent increase in LDH	283
4	Hb decrease or increased RBC transfusion requirement	252
5	Sudden and persistent increase in BUN or creatinine	240
6	Direct antiglobulin test negative	235
7	Refractoriness to platelet transfusions	222
8	Neurologic abnormality	218
9	Decreased haptoglobin	199
10	Reticulocyte increase	178
11	Exclusion of disseminated intravascular coagulation	161
12	Exclusion of high levels of cyclosporine A	153
13	Increased free hemoglobin	146
14	Exclusion of veno-occlusive disease	142
15	Exclusion of aspergillosis	141
16	Exclusion of graft-versus-host disease	139
17	ADAMTS13 decreased or absent	137
18	Renal pathology demonstrating thrombotic microangiopathy	136
19	Decrease of the large fraction of vWF-multimeric pattern	132
20	Exclusion of disease relapse	122
21	Exclusion of active cytomegalovirus disease	111
22	Exclusion of adenovirus	108
23	Exclusion of collagen vascular disease	102
24	Exclusion of malignant hypertension	100
25	Exclusion of human herpes virus 6	90
26	Refractoriness to plasma exchange/FFP replacement	87
27	Exclusion of parvovirus B19	81

Ruutu et al, Haematologica 2007

Transplant-associated microangiopathies (TAM)

Diagnostic criteria and clinical presentation

Table 1. Current diagnostic guidelines for TA-TMA

Category	Blood and Marrow Transplant Clinical Trials Network[18]	International Working Group of the European Group for Blood and Marrow Transplantation[58]	Probable TMA as defined by validation study by Cho et al[53]
Schistocytes	≥ 2 per high-power field in peripheral blood	> 4% in peripheral blood	≥ 2 per high-power field in peripheral blood
LDH	Increased above institutional baseline	Sudden and persistent increase	Increased
Renal function	Doubling of serum creatinine or 50% decrease in creatinine clearance from baseline before transplantation		
Platelets		Thrombocytopenia: < 50×10^9/L or a ≥ 50% decrease in platelet count	Thrombocytopenia: < 50×10^9/L or a ≥ 50% decrease in platelet count
Red cells		Decreased hemoglobin or increased red blood cell transfusions	Decreased hemoglobin
CNS	Unexplained neurologic dysfunction		
Coombs test	Negative direct and indirect		Negative
Haptoglobin		Decreased	Decreased
Other			No coagulopathy

Reprinted by permission from Wolters Kluwer Health.[53]

Triggers

- **Conditioning regimen: TBI, busulfan, etc**
- **Infections: Aspergillus, HSV, CMV, etc**
- **Immunosuppression: CNI, mTOR inhibit.**
- **GvHD**
- **Complement dysfunction/dysregulation?**

Promoting factors

?

Multifactorial systemic endothelitis

Laskin et al, Blood 2011; Ricklin and Cines, Blood 2013

Review article

Small vessels, big trouble in the kidneys and beyond: hematopoietic stem cell transplantation–associated thrombotic microangiopathy

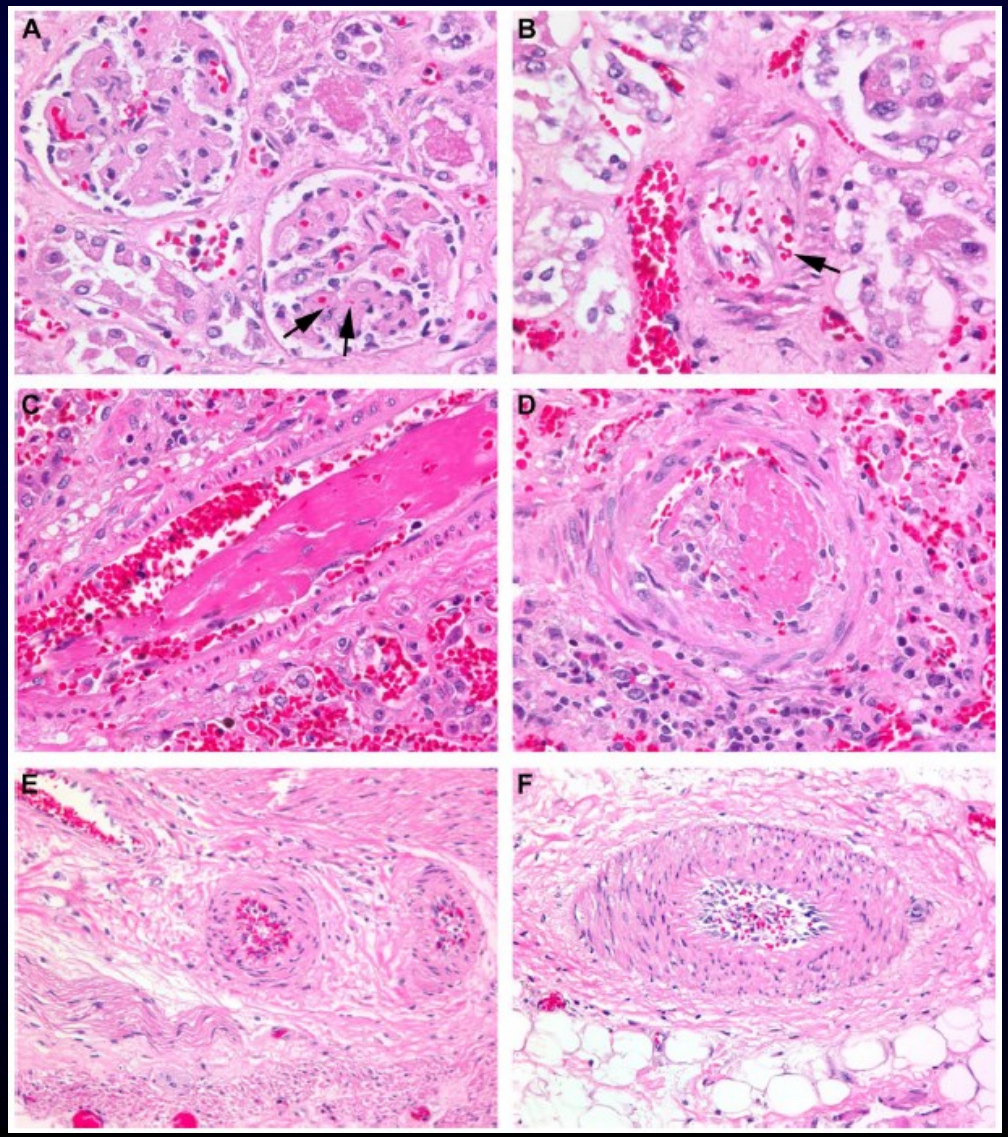
Benjamin L. Laskin,[1] Jens Goebel,[1] Stella M. Davies,[2] and Sonata Jodele[2]

Systemic endothelial damage and red cell extravasation

Renal cortex and glomeruli

Lung arteriole

Mesenteric arteriole



Renal glomerule and arteriole

Pulmunary arteriole

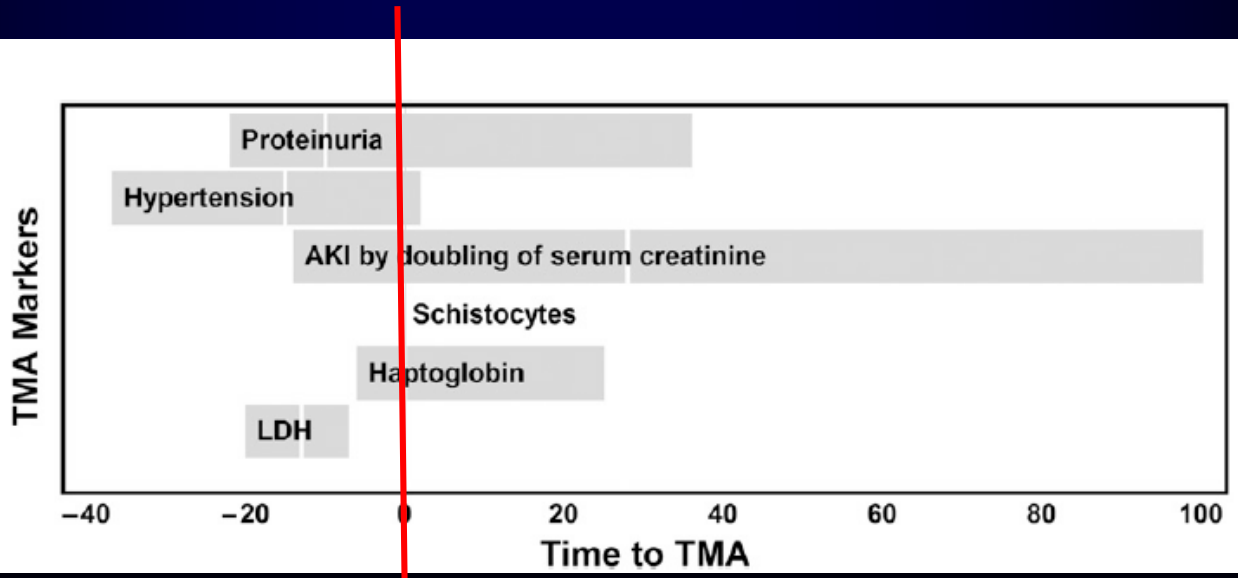
Mesenteric arteriole

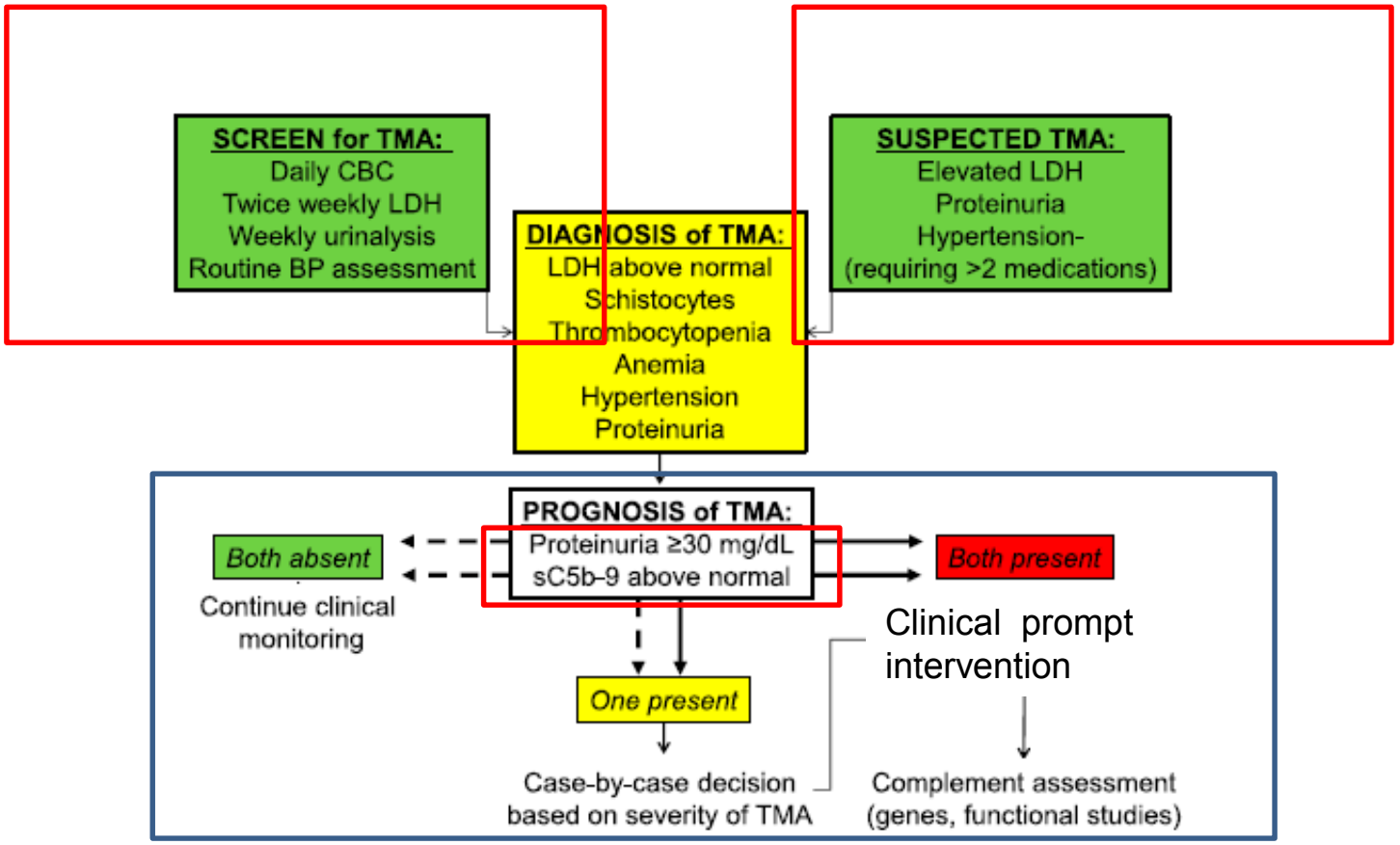
blood
2014 124: 645-653
doi:10.1182/blood-2014-03-564997 originally published online May 29, 2014

Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: a study in children and young adults

Sonata Jodele, Stella M. Davies, Adam Lane, Jane Khoury, Christopher Dandoy, Jens Goebel, Kasiani Myers, Michael Grimley, Jack Bleesing, Javier El-Bietar, Gregory Wallace, Ranjit S. Chima, Zachary Paff and Benjamin L. Laskin

Proteinuria ≥30 mg/dL	26 (66.7%)	16 (31.4%)	<.01
Proteinuria lasting >2 wk	25 (64.1%)	15 (29.4%)	<.01
Urine protein/creatinine ratio	2.8 [1.0-3.9]	0.8 [0.4-2.0]	.02
Subjects with elevated sC5b-9	26/39 (67%)	4/20 (20%)	<.01





Low risk TMA
OS 100%

High risk TMA
OS < 20%

BLOOD, 24 JULY 2014 • VOLUME 124, NUMBER 4

THROMBOSIS AND HEMOSTASIS

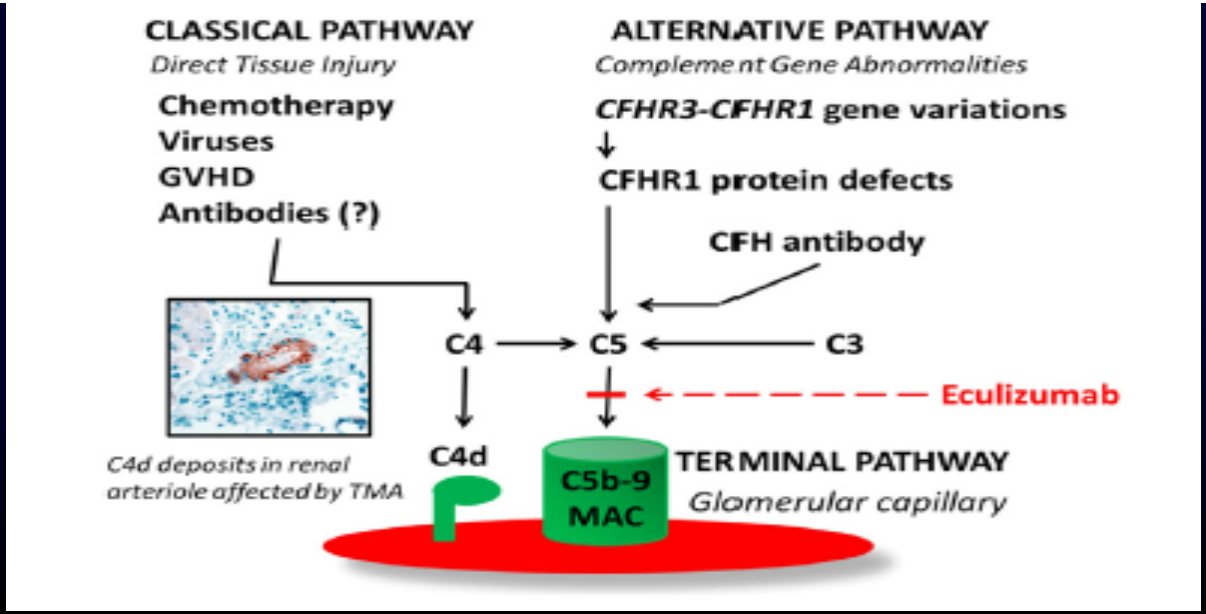
Abnormalities in the alternative pathway of complement in children with hematopoietic stem cell transplant-associated thrombotic microangiopathy

Sonata Jodele,[1] Christoph Licht,[2] Jens Goebel,[3] Bradley P. Dixon,[3] Kejian Zhang,[4] Theru A. Sivakumaran,[4] Stella M. Davies,[1] Fred G. Pluthero,[2] Lily Lu,[2] and Benjamin L. Laskin[5]

Table 2. Complement system analysis in patients with HSCT-TMA

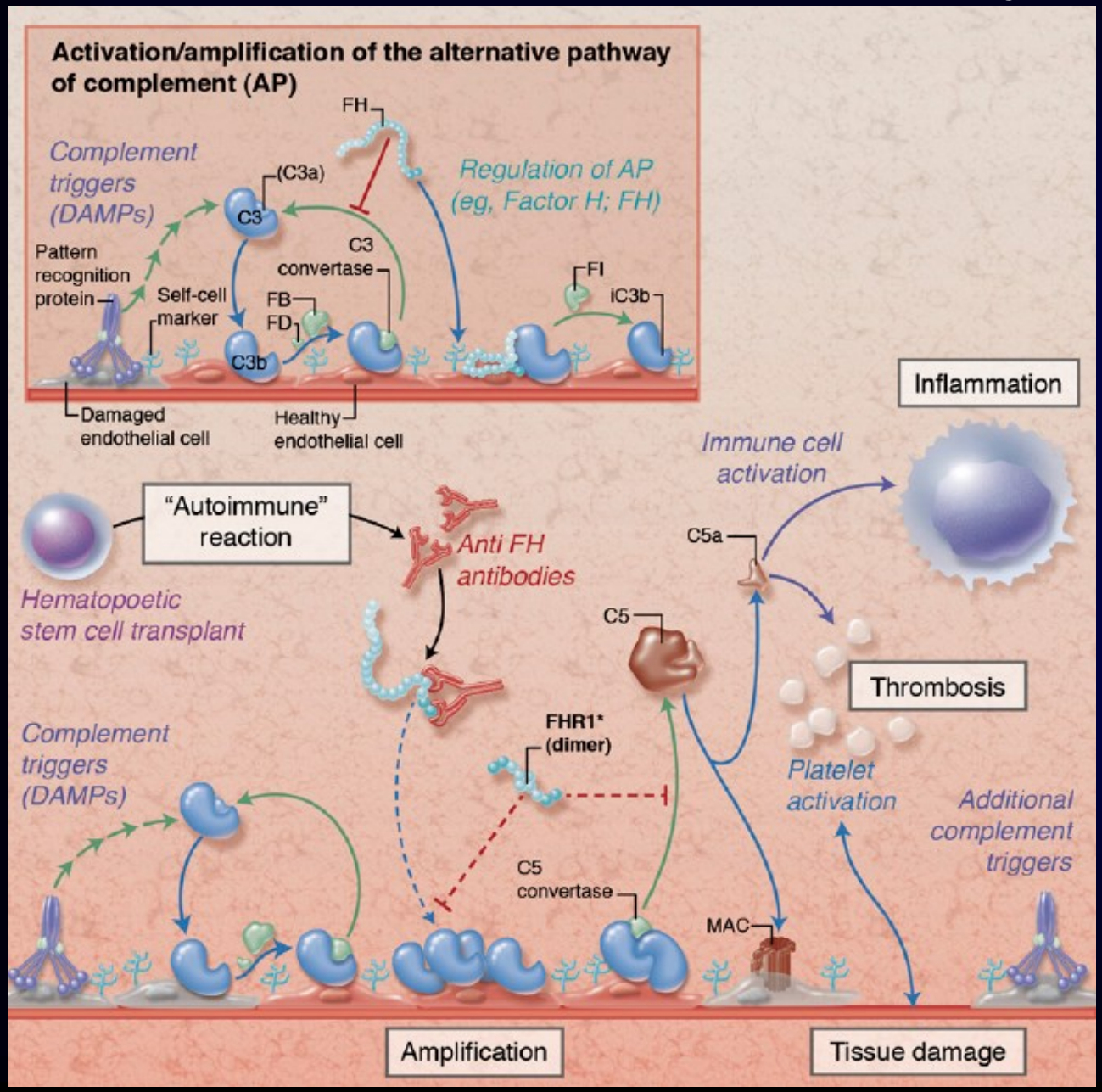
Patient	Transplant type	*CFI,CFH,MCP,CFB,CFR5* (direct sequence analysis)	Recipient *CFH-CFHR5* (MLPA)	Donor *CFH-CFHR5* (MLPA)	CFH antibody (ELISA)	CFHR1 protein analysis (western blot)
1	autologous	normal alleles	**del(CFHR3-CFHR1)*	n/a	absent	present
2	autologous	normal alleles	**del(CFHR3-CFHR1)*	n/a	absent	present
3	autologous	normal alleles	**del(CFHR1-CFHR4)*	n/a	absent	present
4	allogeneic	normal alleles	**del(CFHR3-CFHR1)*	normal allele	present	present
5	allogeneic	normal alleles	**del(CFHR3-CFHR1)*	**del(CFHR3-CFHR1)*	present	present
6	allogeneic	normal alleles	normal allele	normal allele	present	present

CFR, complement factor H-related gene 5.
**del* refers to heterozygous deletions.



Transplant-associated microangiopathies (TAM or TA-TMA)

Complement-mediated pathophysiology



Ricklin and Cines, Blood 2013

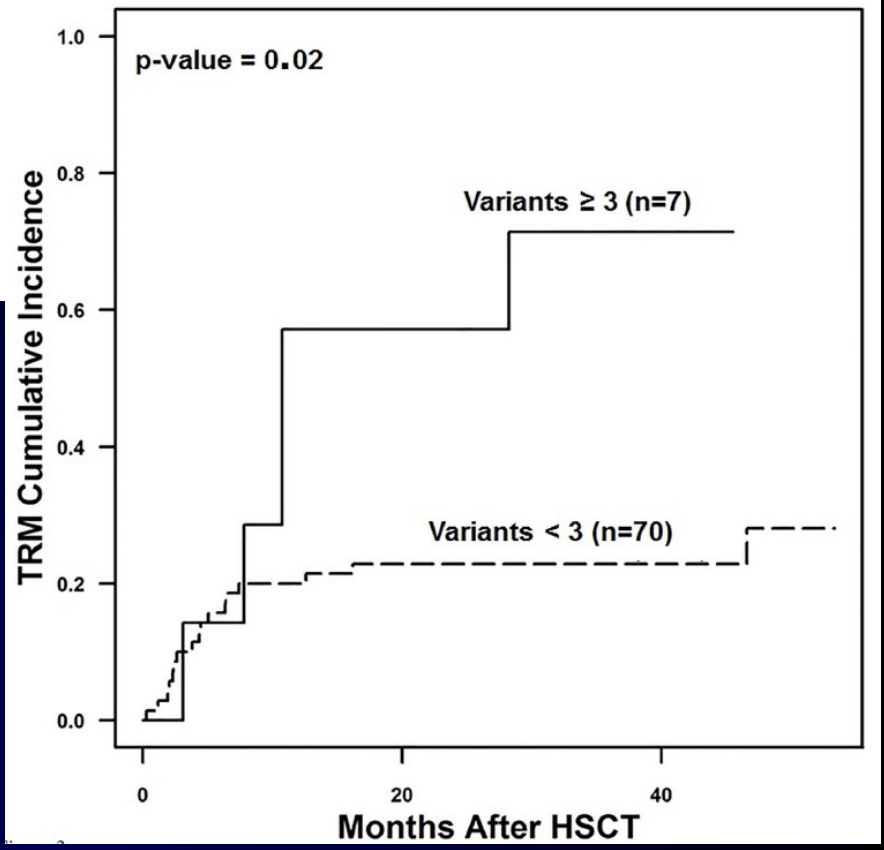
blood

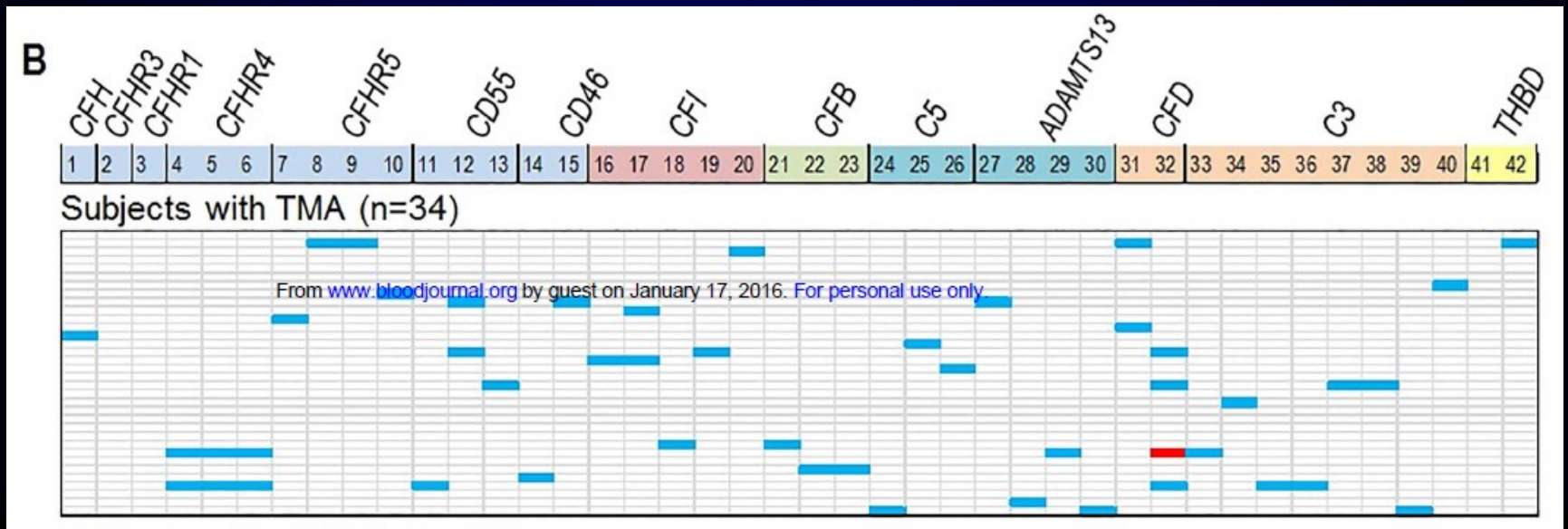
Prepublished online November 24, 2015;
doi:10.1182/blood-2015-08-663435

The genetic fingerprint of susceptibility for transplant associated thrombotic microangiopathy

Sonata Jodele, Kejian Zhang, Fanggeng Zou, Benjamin Laskin, Christopher E. Dandoy, Kasiani C. Myers, Adam Lane, Jaroslav Meller, Mario Medvedovic, Jenny Chen and Stella M. Davies

- ✓ 17 candidate complement related genes studied in HSCT (n=77; n=34 TA-TMA)
- ✓ Gene variants (1 or >1) found in 56% of TA-TMA vs 9% of non-TMA (p<0.0001); 3 or >3 variants (found only in non-caucasian) associated with higher TRM (71%)
- ✓ Functional complement derangement demonstrated in pre-HSCT samples of patients with gene variants
- ✓ *Genetic predisposition to TA-TMA?*





Transplant-associated microangiopathies (TAM or TA-TMA)

Prophylaxis and treatment

Prophylaxis

- ✓ No effective prophylaxis
- ✓ Early diagnosis for early (pre-emptive?) treatment

Treatment

- ✓ No established treatment
- ✓ Different strategies (even in combination)
  - ✓ Best supportive care (…)
  - ✓ Withdrawal of offending causative agents (e.g., CNI)
  - ✓ Treatment of concomitant conditions (e.g., GvHD, infections, hypertension, etc)
  - ✓ Etiologic/pathogenic treatment?

Treatment of transplant-associated microangiopathies

Etiologic treatment

No effect:

- **Corticosteroids**
- **Antifibrinolytics**
- Prostacyclin infusions
- Eparin
- Vincristine
- Thrombolitic therapy
- **i.v. immunoglobulins**
- Splenectomy
- Daclizumab

Potential Efficacy:

- **Plasmapheresis***
- **Daclizumab**
- **Rituximab**

Few cases

- **Defibrotide**
- **Eculizumab**

*= generally not effective, Choi et al Drugs 2009

Uderzo C et al., J Bone Marrow Res 2014; Uderzo et al , BMT 2000; Sarode *et al*, BMT 1995; Roy *et al*, BMT 2001; Holler *et al*, Blood 1989; Fuge *et al*, BJH 2001; Corti *et al,* BMT 2002; Au *et al*, BJH 2007

Journal of Bone Marrow Research

Uderzo et al., J Bone Marrow Res 2014, 2:3
http://dx.doi.org/10.4172/2329-8820.1000152

Review Article Open Access

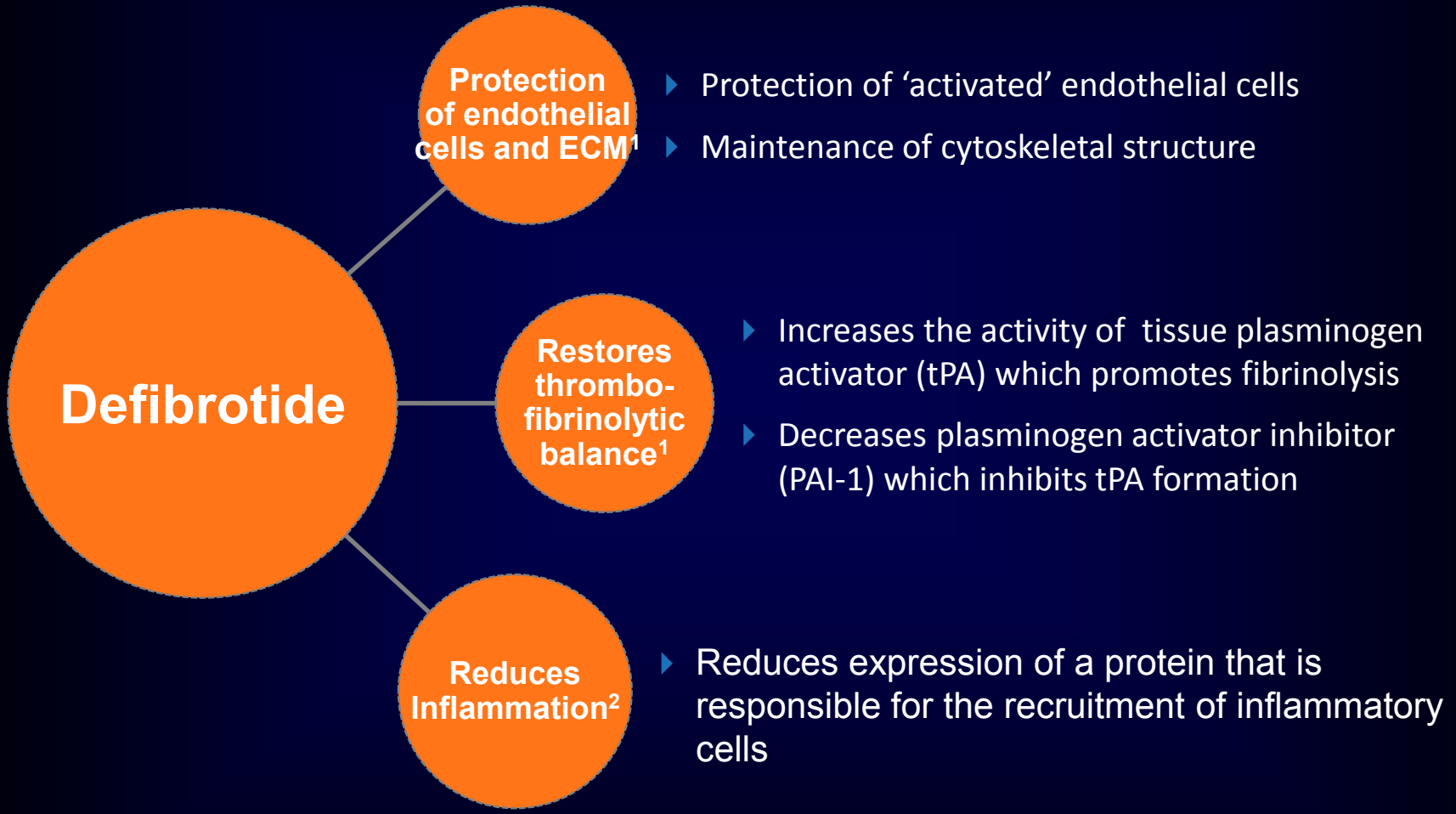
Transplant-Associated Thrombotic Microangiopathy (TA-TMA) and Consensus Based Diagnostic and Therapeutic Recommendations: Which TA-TMA Patients to Treat and When?

Cornelio Uderzo C[1*], Sonata Jodele[2], Mohamed El Missiry[3], Fabio Ciceri[4], Alessandro Busca[5], Andrea Bacigalupo[6] and Selim Corbacioglu[7]

Proposed treatments	
A) Defibrotide Treatment	Induction: 25 mg/kg/day /iv. in 4 divided doses for at least 4 to 6 weeks (i.e. until 2 weeks of "TA-TMA complete remission") Consolidation (beyond 6 weeks) for poor responders: should be discussed with the coordinating investigator
B) Terminal complement blocking therapy (Eculizumab)	Induction dose (i.e 300 mg iv.between 5 to 10 Kg /BW, until 900 mg iv. between 40 kg / BW and over), Maintenance dose (i.e 300 mg iv. every 2 weeks if patient weight is between 5 to 10 Kg, until 1200 mg iv. every 2 weeks if patient weight is 40 kg or over) Eculizumab dosing schedule will be used with dose adjustments guided by pharmacodynamic monitoring of complement blockage and clinical response (i.e. until 3-4 treatments with sC5b-9 and CH50 normalization)

Plasma-exchange?

Mechanisms of action of defibrotide



1. Defitelio® Summary of Product Characteristics.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002393/WC500153150.pdf;
2. Richardson PG et al. *Expert Opin Drug Saf* 2013;12:123–136

Defibrotide for the treatment of TA-TMA

DF 40 mg/Kg (os) for 41 days

- 12 pts
- CR: 5 pts
- PR 3 pts
- Stable 1 pt
- NR 3 pts

Corti P, BMT 2002, 29

Table IV. Defi

Study	ose	Response
Wolff et al.[75]		CR
		NC
		CR
Besisik et al.[11		CR
Corti et al.[125]		CR
		CR

Table 1 Patients, TTP characteristics and outcome

Patients	*Sex*	*Age years*	*Diagnosis at BMT*	*BMT type*	*TTP index*	*LDH max*[a]	*TTP grade*	*Symptoms*	*DFT therapy (days)*	*No. of plasma phereses*	*Outcome*		*Cause of death*
											TTP	*Patients*	
1	M	3	AML (1st CR)	Rel	<20	2t	mild	—	17	—	TR	alive	—
2	M	1	FEL	Unrel	>20	3t	severe	SHS	51	—	TR	alive	—
3	M	12	ALL (2nd CR)	Rel	>20	2t	severe	SHS	98	—	TR	alive	—
4	F	7	ALL (3rd CR)	Unrel	>20	5t	severe	SHS	61	—	TR[b]	alive	—
5	F	35	CML (1st CP)	Unrel	>20	7t	severe	CNS	23	2	NR	dead	PC
6	F	16	ALL (3rd CR)	Unrel	>20	2t	severe	—	46	2	PR	dead	PD
7	M	33	HL (PD)	Rel	>20	2t	severe	K,SHS	30	—	TR	alive	—
8	M	20	ALL (3rd CR)	Unrel	>20	2t	severe	CNS, SHS	17	3	NR	dead	IP
9	M	35	ALL (2nd CR)	Unrel	>20	5t	severe	—	34	—	PR	dead	PG
10	F	37	AML (1st CR)	Rel	<20	2t	mild	—	38	—	TR	alive	—
11	F	55	CML (1st CP)	Rel	>20	1t	severe	SHS	64	2	NR	dead	GG
12	F	30	AML (PD)	Unrel	>20	2t	severe	SHS	41	3	PR	dead	IP

Cas t (M N Myeloma)

9 months p
TMA with
involvm

bjh correspondence

Successful use of eculizumab in a patient with post-transplant thrombotic microangiopathy

Transplantation-associated thrombotic microangiopathy (TA-TMA) represents a challenge after allogeneic haematopoietic stem cell transplantation (HSCT) because of diagnostic uncertainties, lack of established treatment, and an overall poor prognosis (Laskin *et al*, 2011). We report the case of a 61-year-old man who was diagnosed with multiple myeloma in 2009. He was initially treated with a combination of bortezomib, doxorubicin and dexamethasone, followed by high-dose melphalan with autologous HSCT. Following disease relapse in 2011, he received three courses of bortezomib, thalidomide dexamethasone, and was then included in a sequential autologous-allogeneic tandem approach that comprised high-dose melphalan and auto-HSCT followed by two Gray total body irradiation-conditioned allo-HSCT (Karlin *et al*, 2011). Two months post-HSCT, the patient was diagnosed with graft-versus-host disease (GvHD) of the skin (stage 3) and gut (stage 1), which responded to methylprednisone 2 mg/kg. Three months later, GvHD of the gut reappeared during steroid tapering. Although the GvHD responded to the increased doses of steroids, the patient developed a severe TA-TMA (Fig 1). As already reported in such a situation, acute renal failure was absent (Cho *et al*, 2010). A concomitant diagnosis of cytomegalovirus (CMV) & Epstein Barr virus (EBV) infections was made. Ciclosporin was stopped, treatment with Foscanet was initiated and the patient received one injection of mabthera. Seven days later, he developed a progressive involvement of the central nervous system, with confusion and peripheral facial paralysis, while the biological characteristics of TA-TMA remained stable (Fig 1). Ciclosporin was no longer detectable in the blood. CMV & EBV infections responded to treatment at that time. Magnetic resonance imaging and a lumbar puncture were normal. Complement proteins (C3, C4, Factor H, Factor I) were in the normal ranges. Testing for anti-complement Factor H antibodies was negative. No decrease in ADAMTS 13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity was identified. Given the devastating prognosis, we administered eculizumab to this patient accordingly to atypical haemolytic and uraemic syndrome dosage (900 mg weekly for four weeks, followed by 1200 mg every two weeks). The patient's neurological status improved dramatically within 48 h after the first infusion of eculizumab. Clinical improvement was associated with rapid normalization of disease activity markers: platelet counts increased, and lactate dehydrogenase levels decreased quickly (Fig 1). Complete C5 blockage, defined by a 50% haemolytic complement (CH_{50}) activity below 10% was observed 24 h after the first infusion of eculizumab and during the entire study period. Concomitantly, the number of circulating endothelial cells (CEC), a known prognostic marker in thrombotic microangiopathy (Erdbruegger *et al*, 2006), decreased drastically. The levels of CEC were about 1200/ml before eculizumab infusion compared with 512/ml at 36 h and 5/ml at 3 days post-injection. The patient was discharged two weeks later with normal neurological status. Three months later, eculizumab treatment was stopped because there were no signs of TMA. After a 3-month follow-up period, the patient had completely recovered and continues to do very well. Given the progressive course of the disease after the mabthera injection, it seemed unlikely that the recovery was due to this treatment. The rapid clinical response to eculizumab supports the concept that TA-TMA might involve aberrant and autonomous complement activation despite the control of the potential causes (calcineurin inhibitors, GvHD & herpes virus infections). The dramatic resolution of symptoms after eculizumab administration suggests that TA-TMA is an area deserving further careful investigation of therapeutic complement blockade.

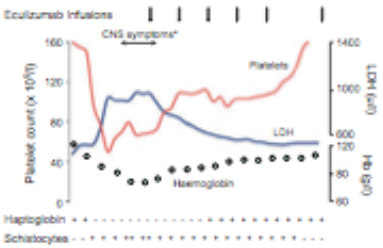


Fig 1. Clinical and biological response to eculizumab therapy in a patient with transplantation-associated thrombotic microangiopathy (TA-TMA) post- haematopoietic stem cell transplantation (HSCT) with central nervous system involvement. The figure shows data indicating rapid clinical improvement after the administration of monoclonal C5 antibody eculizumab in a 61-year-old patient with TA-TMA post-haematopoietic stem cell transplantation (HSCT), resulting in central nervous system involvement. There was also a rapid normalization in platelet counts and lactate dehydrogenase (LDH) levels.

British Journal of Haematology, 2013, **161**, 279–298

LDH (UI)

Platelets (x10³/mm³)

Hb (g/dL)

Courtesy of Regis Peffault de Latour

Original Clinical Science—General

(*Transplantation* 2015;99: 1953–1959)

Use of Eculizumab in Patients With Allogeneic Stem Cell Transplant-Associated Thrombotic Microangiopathy: A Study From the SFGM-TC

Flore Sicre de Fontbrune,[1] Claire Galambrun,[2] Anne Sirvent,[3] Anne Huynh,[4] Stanislas Faguer,[5] Stephanie Nguyen,[6] Jacques-Olivier Bay,[7] Bénédicte Neven,[8] Julie Moussi,[9] Laurence Simon,[10] Alienor Xhaard,[1] Matthieu Resche-Riggon,[11] Alix O'Meara,[1] Veronique Fremeaux-Bacchi,[12] Agnes Veyradier,[13] Gérard Socié,[1] Paul Coppo,[14] and Régis Peffaut de Latour[1]

Eculizumab® start in post allo TMA, N = 12

Induction

Eculizumab® stop, n=5

- Failure and death, n=3
- Progressive severe aGvHD with or without relapse, and death n=2

N = 7

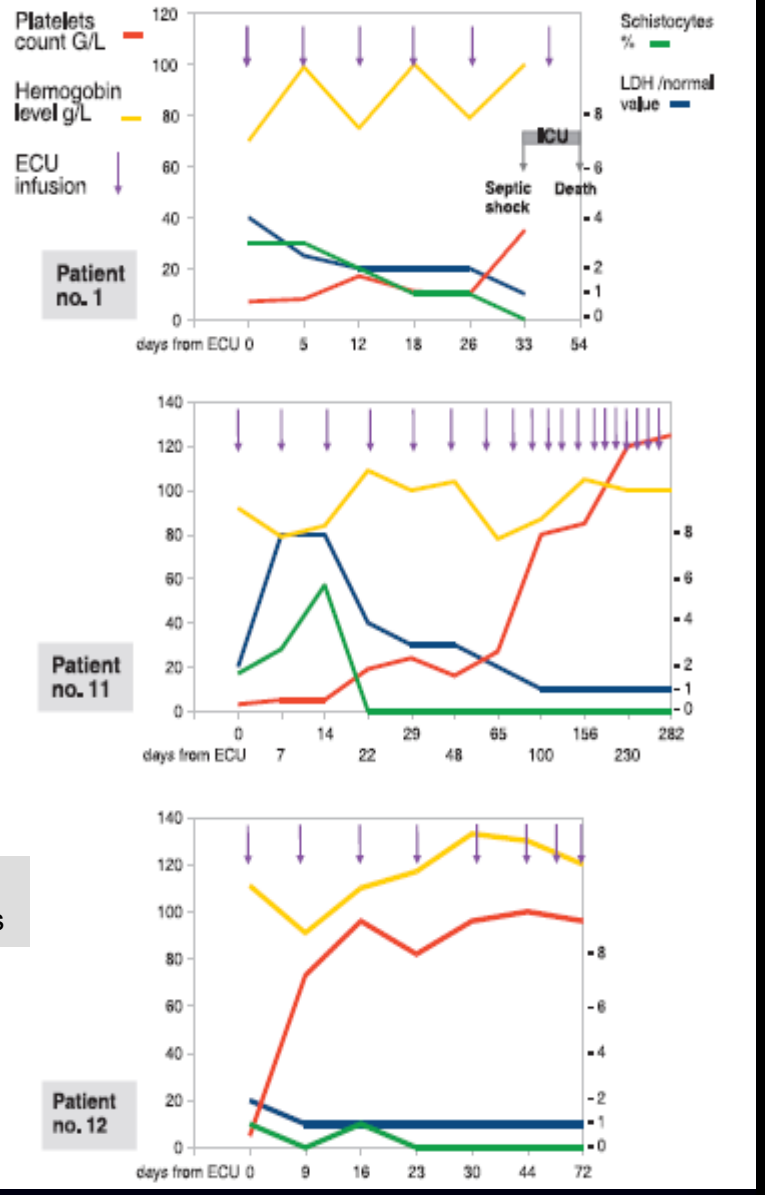
Maintenance

Eculizumab® stop, n=6

- Failure and death, n=2
- Failure and alive, n=1
- Response and death n=1
- Response and alive, n=2

Responding (on therapy at day 70) n=1

900 mg every week during 4 weeks, followed by a maintenance dose of 1200 mg every 14 days



In summary, Eculizumab achieved an overall hematological response rate of 50% (6/12) and an overall survival rate of 33% (4/12) with a median follow-up of 432 days.

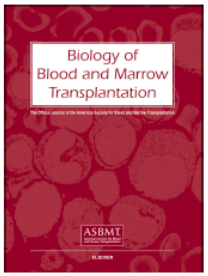
Eculizumab Therapy in Children with Severe Hematopoietic Stem Cell Transplantation–Associated Thrombotic Microangiopathy

Sonata Jodele [1,*], Tsuyoshi Fukuda [2], Alexander Vinks [2], Kana Mizuno [2], Benjamin L. Laskin [3], Jens Goebel [4], Bradley P. Dixon [4], Ashley Teusink [5], Fred G. Pluthero [6], Lily Lu [6], Christoph Licht [6], Stella M. Davies [1]

BBMT 2014

Accepted Manuscript

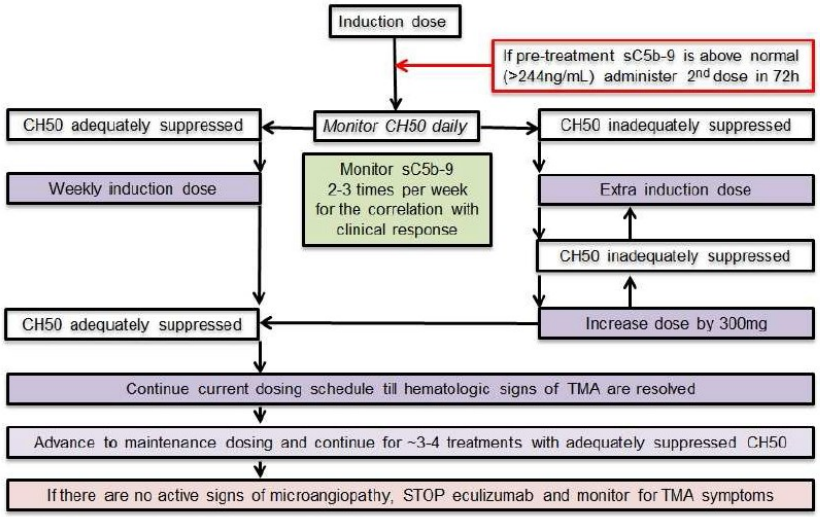
BBMT 2015



Variable eculizumab clearance requires pharmacodynamic monitoring to optimize therapy for thrombotic microangiopathy after hematopoietic stem cell transplantation

Sonata Jodele, Tsuyoshi Fukuda, Kana Mizuno, Alexander A. Vinks, Benjamin L. Laskin, Jens Goebel, Bradley P. Dixon, Ranjit S. Chima, Russel Hirsch, Ashley Teusink, Danielle Lazear, Adam Lane, Kasiani C. Myers, Christopher E. Dandoy, Stella M. Davies

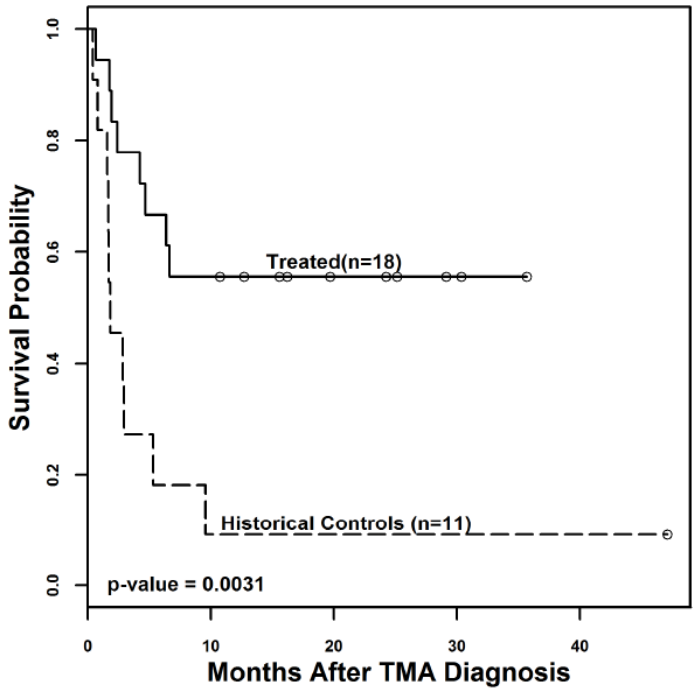
A

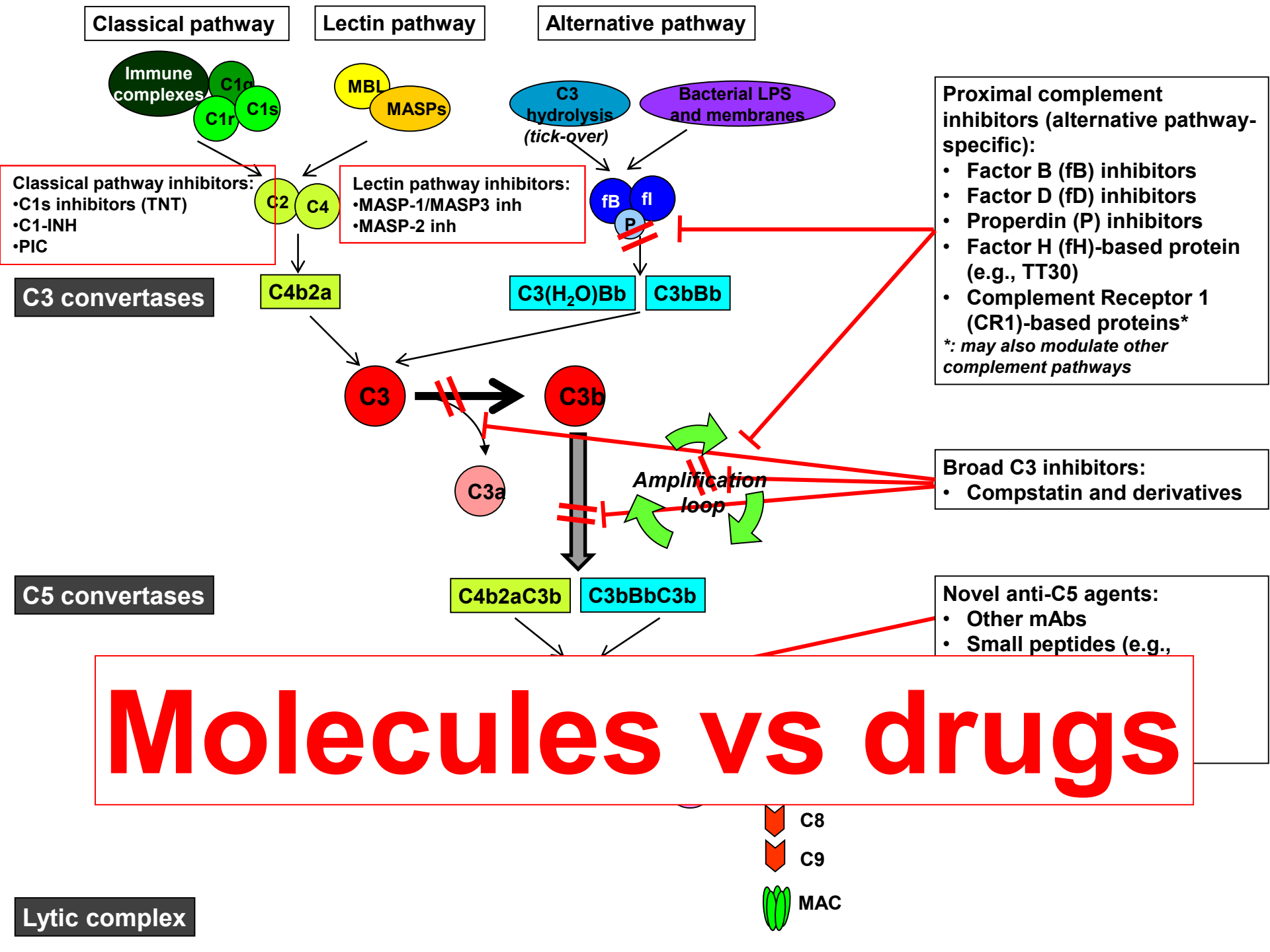


Adequate CH50 suppression is serum CH50 level <10% of normal

B

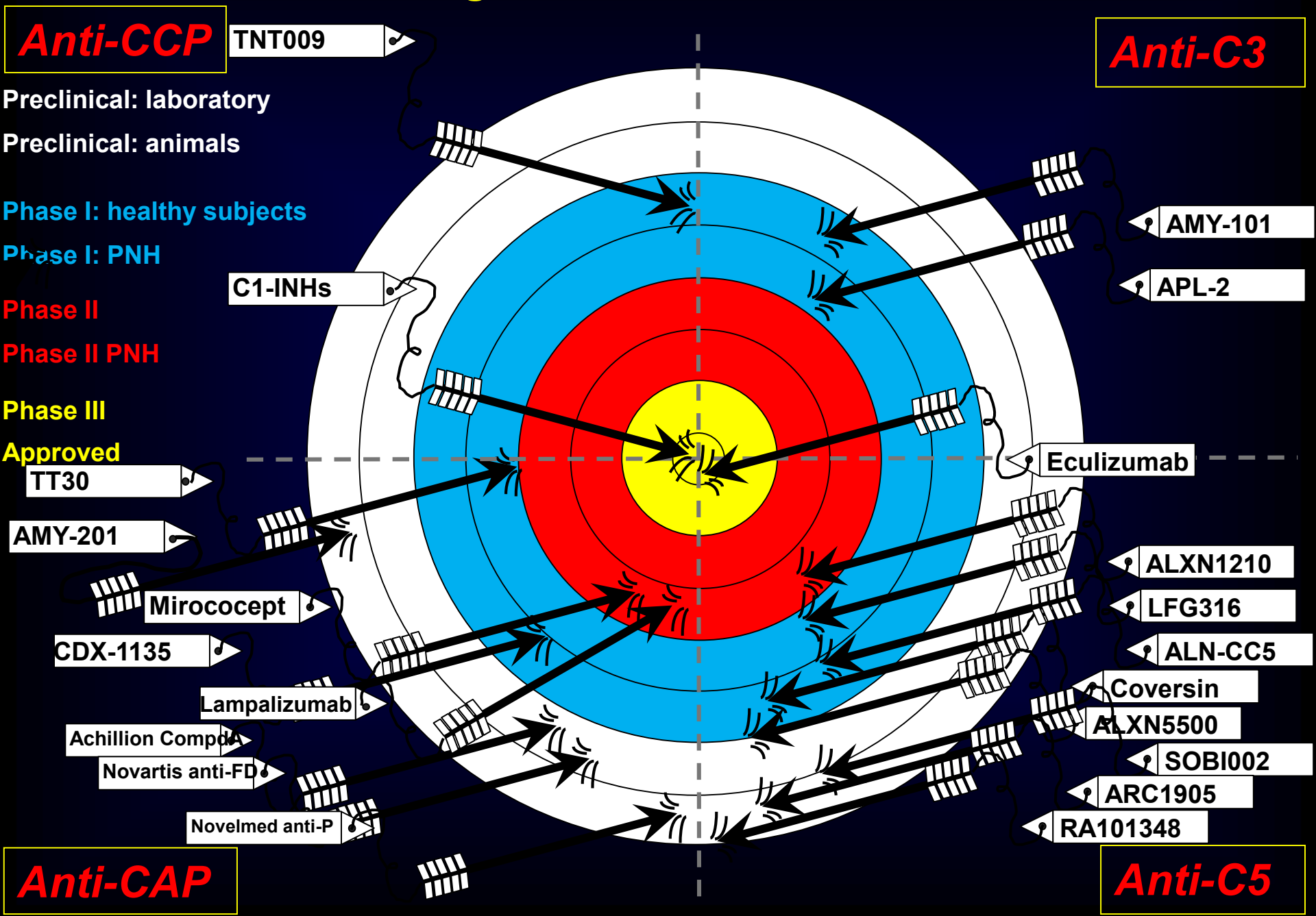
Patient weight	*Induction dose*	*Maintenance dose*
40 kg and over	*900 mg*	*1200 mg every 2 weeks*
30 kg to less than 40 kg	*600 mg*	*900 mg every 2 weeks*
20 kg to less than 30 kg	*600 mg*	*600 mg every 2 weeks*
10 kg to less than 20 kg	*600 mg*	*300 mg every 2 weeks*
5 kg to less than 10 kg	*300 mg*	*300 mg every 2 weeks*





Molecules vs drugs

The target of clinical translation



Thanks to: Anna Paola Iori

Thank you!