



# ENDOTHELIPATHIES - TA-TMA AND SOS

Dr Sachin Punatar

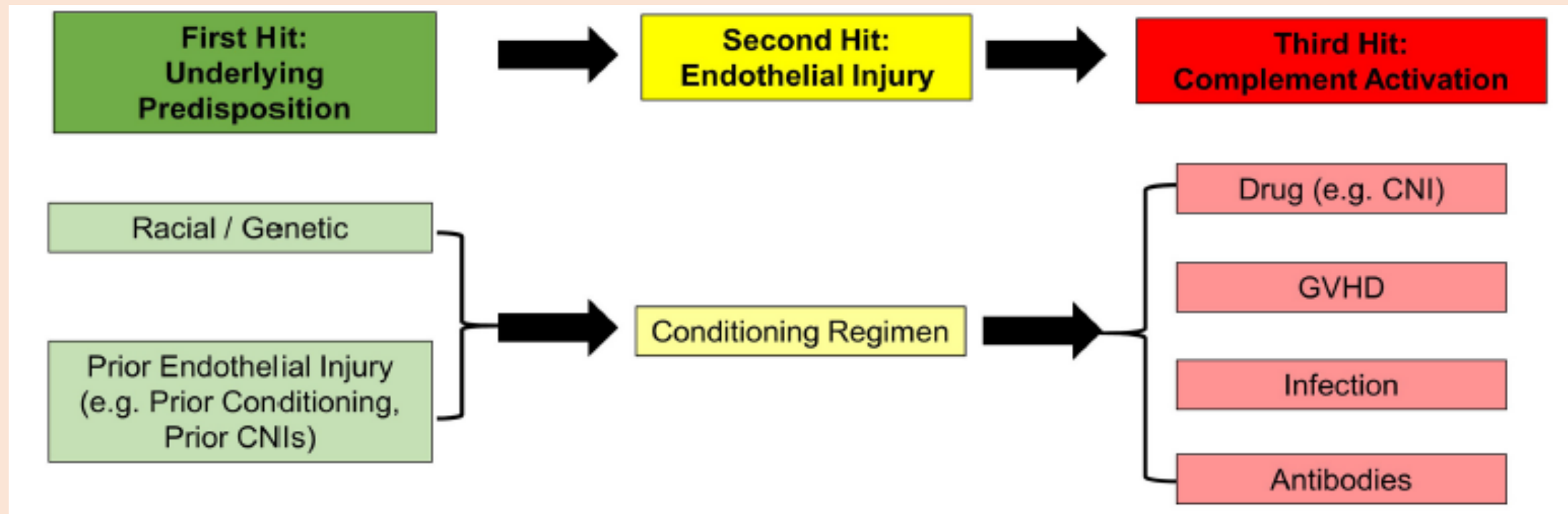
Professor, Stem Cell Transplant Unit,  
Department of Medical Oncology  
ACTREC, Tata Memorial Centre

# SECTION – 1 – TA-TMA

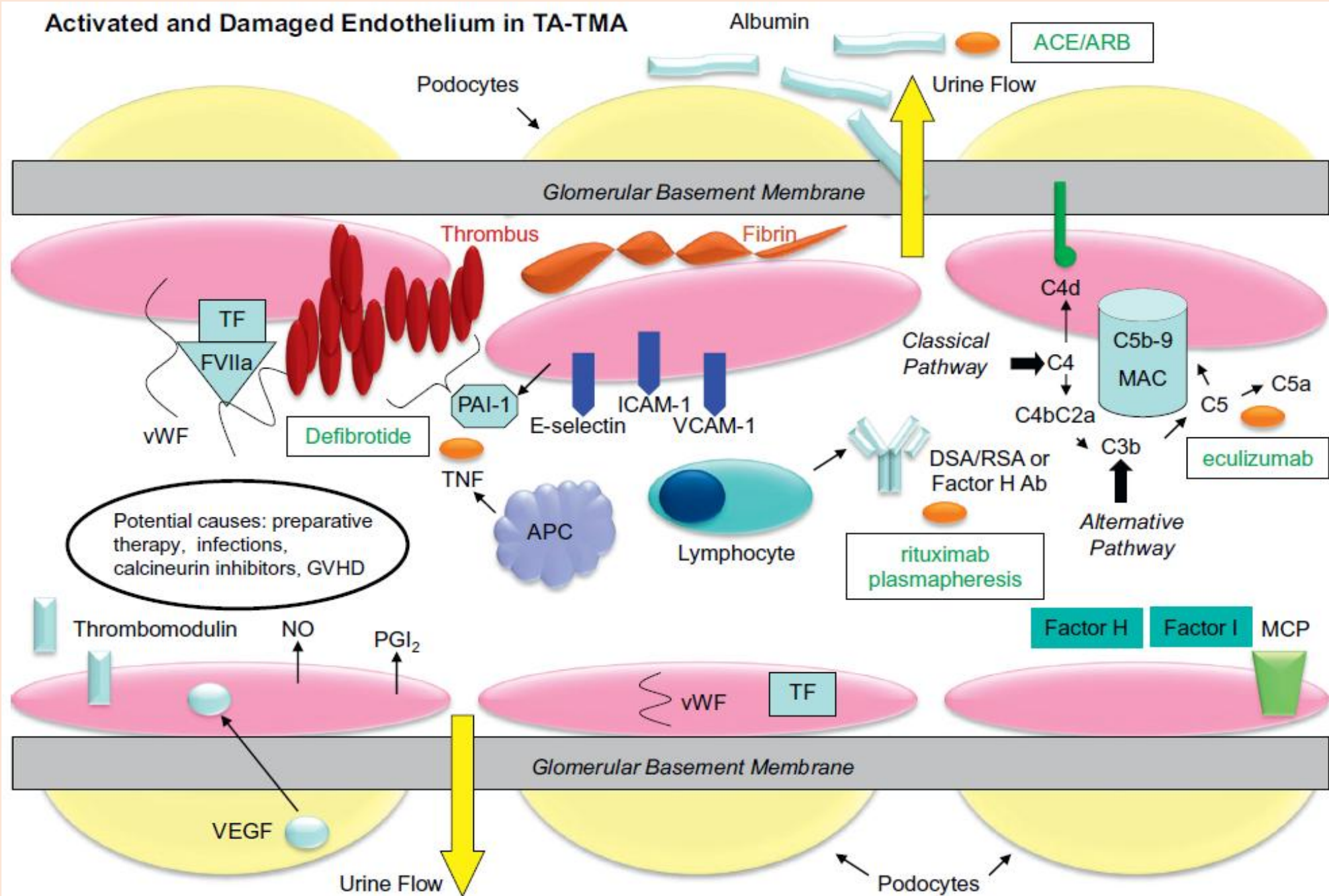
# INTRODUCTION

- TA-TMA – life threatening acute complication post HSCT
- Variably reported incidence – 10 – 35%
- Multi system involvement
- High mortality - >90% in patients with severe forms of TMA

# PATHOGENESIS



# Activated and Damaged Endothelium in TA-TMA



Normal Endothelium

# DIAGNOSIS

- Lack of a uniform diagnostic criteria
- >25 proposed criteria
- Key reason behind variably reported incidence and risk factors for TMA

# Definitions of TA-TMA

- Definitive TA-TMA – BMT – CTN criteria
- Probable TMA – Cho criteria

BMT – CTN Criteria	Cho criteria
Schistocytes $\geq 2$ / HPF	Schistocytes $\geq 2$ / HPF
Elevated LDH	Elevated LDH
Renal compromise	No coagulopathy
Unexplained neurological manifestations	Drop in Hb and platelets
Negative Coomb's test	Negative Coomb's test



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# Transplantation and Cellular Therapy

journal homepage: [www.tctjournal.org](http://www.tctjournal.org)



American Society for  
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## Guideline

# Harmonizing Definitions for Diagnostic Criteria and Prognostic Assessment of Transplantation-Associated Thrombotic Microangiopathy: A Report on Behalf of the European Society for Blood and Marrow Transplantation, American Society for Transplantation and Cellular Therapy, Asia-Pacific Blood and Marrow Transplantation Group, and Center for International Blood and Marrow Transplant Research



M.L. Schoettler<sup>2</sup>, E. Carreras<sup>3</sup>, B. Cho<sup>4</sup>, C.E. Dandoy<sup>5</sup>, V.T. Ho<sup>6</sup>, S. Jodele<sup>5</sup>, I. Moissev<sup>7</sup>, I. Sanchez-Ortega<sup>8</sup>, A. Srivastava<sup>9</sup>, Y. Atsuta<sup>10</sup>, P. Carpenter<sup>11</sup>, J. Koreth<sup>6</sup>, N. Kroger<sup>1</sup>, P. Ljungman<sup>12</sup>, K. Page<sup>13</sup>, U. Popat<sup>14</sup>, B.E. Shaw<sup>13</sup>, A. Sureda<sup>15</sup>, R. Soiffer<sup>6</sup>, S. Vasu<sup>1,\*</sup>

TMA Harmonization Panel Consensus Recommended Diagnostic Criteria, Modified Jodele Criteria

Biopsy-proven disease (kidney or GI) or	
Clinical criteria: must meet $\geq 4$ of the following 7 criteria within 14 days at 2 consecutive time points	
Anemia*	<p>Defined as one of the following:</p> <ol style="list-style-type: none"> <li>1. Failure to achieve transfusion independence for pRBCs despite evidence of neutrophil engraftment</li> <li>2. Hemoglobin decline from patient's baseline by 1 g/dL</li> <li>3. New onset of transfusion dependence</li> </ol> <p><i>Rule out other causes of anemia, such as AIHA and PRCA</i></p>
Thrombocytopenia*	<p>Defined as one of the following:</p> <ol style="list-style-type: none"> <li>1. Failure to achieve platelet engraftment</li> <li>2. Higher than expected platelet transfusion needs</li> <li>3. Refractoriness to platelet transfusions</li> <li>4. 50% reduction or greater in baseline platelet count after full platelet engraftment</li> </ol>
Elevated LDH	>ULN for age
Schistocytes	Present
Hypertension	>99th percentile for age (<18 yr), or systolic BP $\geq 140$ mmHg or diastolic BP $\geq 90$ mmHg ( $\geq 18$ yr)
Elevated sC5b-9	$\geq$ ULN
Proteinuria	$\geq 1$ mg/mg rUPCR

- Usually diagnosed at about 1-2 months post BMT
- Nearly 90% cases within day+100
  
- Classic “TMA Triad”
  - Hypertension
  - Thrombocytopenia
  - Elevated LDH
  
- Present in >90% patients with TMA

**Table 3. Clinical Presentations of TA-TMA**

<i>System</i>	<i>Clinical presentations</i>
Renal	Acute kidney injury, chronic kidney disease, proteinuria or hypertension
Pulmonary	Pulmonary hypertension, pleural effusion
Gastrointestinal	Diarrhea, vomiting, abdominal pain or intestinal bleeding, ascites
Neurological	Confusion, headache, hallucinations or seizures
Polyserositis	Pericardial effusion, pleural effusion, ascites

Abbreviation: TA-TMA = transplantation-associated thrombotic microangiopathy.

# RISK FACTORS

- Variable risk factors reported in different studies
- Acute GVHD
- Haplo-identical transplants
- Calcineurin inhibitors and other drugs
- Infections

## ARTICLE



# Pre-transplant use of tyrosine kinase inhibitors and transplant associated thrombotic microangiopathy - a single centre analysis of incidence, risk factors and outcomes



Sachin Punatar <sup>1,2</sup> · Siddhesh A. Kalantri <sup>1,2</sup> · Akanksha Chichra<sup>1,2</sup> · Amit Kumar Agrawal<sup>1</sup> · Lingaraj Nayak<sup>1,2</sup> · Avinash Bonda<sup>1,2</sup> · Anant Gokarn<sup>1,2</sup> · Bhausahab Bagal <sup>1,2</sup> · Libin Mathew<sup>1</sup> · Sadhana Kannan<sup>3</sup> · Navin Khattry <sup>1,2</sup>

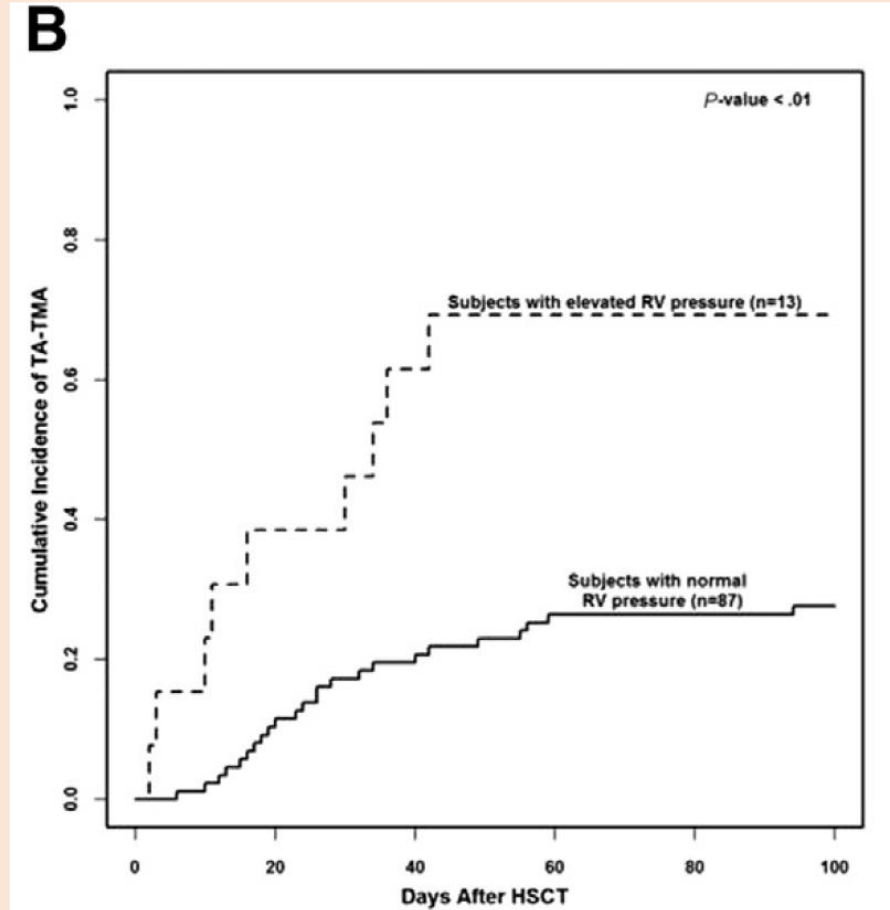
Table 3 Multivariate analysis of risk factors for TA-TMA<sup>a</sup>.

Variable		OR (95% CI)	P Value
Acute GVHD			
Absent	146	1.00	0.003
present	94	4.179 (1.6–10.7)	
Type of transplant			
MSD	174	1.00	–
MUD	16	3.118 (0.7–13.4)	0.127
HAPLO	50	3.164 (1.2–8.2)	0.018
Pre-transplant TKI Use			
No	166	1.00	0.028
Yes	74	2.71 (1.1–6.6)	0.028

# PREDICTIVE AND PROGNOSTIC MARKERS

- Several predictive and prognostic markers evaluated in the last few years
- Radiological and blood-based markers

- Elevated RV pressure on day 7
- Elevated sC5b-9 (baseline, day 28)
- Thrombomodulin
- Calpain
- Haptoglobin degradation products



- 9 of 13 with elevated RV pressure developed TMA (69%)
- 26% in those who did not have elevated RV pressure
- $P=0.004$

# TREATMENT

- Supportive therapies
  - Aggressive control of hypertension
  - Withdraw CNI
  - Treatment of underlying infections or GVHD
  - Managing fluid and electrolyte balance

- Specific therapies
  - Defibrotide
  - TPE +/- Rituximab
  - Eculizumab
  - Narsoplimab

# PROPHYLACTIC STRATEGIES

- Prevention is better (and cheaper) than cure



## Post-transplant conditions

# Oral eicosapentaenoic acid for complications of bone marrow transplantation

H Takatsuka<sup>1</sup>, Y Takemoto<sup>1</sup>, N Iwata<sup>1</sup>, A Suehiro<sup>1</sup>, T Hamano<sup>1</sup>, T Okamoto<sup>1</sup>, A Kanamaru<sup>2</sup>, and E Kakishita<sup>1</sup>

<sup>1</sup>Second Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan; <sup>2</sup>Third Department of Internal Medicine, Kinki University School of Medicine, Osaka, Japan

- Randomized placebo controlled trial
- EPA – 600 mg TDS from day-21 to day+180
- 7 patients in the EPA arm, 9 patients in the placebo group
- 0 TMA in EPA arm, vs 4 of 9 (45%) in the placebo group

721.CLINICAL ALLOGENEIC TRANSPLANTATION: CONDITIONING REGIMENS, ENGRAFTMENT, AND  
ACUTE TRANSPLANT TOXICITIES | NOVEMBER 5, 2020

## **A Pilot Trial of Pre-Transplant Risk Stratification and Prophylactic Defibrotide to Prevent Serious Thrombotic Microangiopathy in High-Risk Pediatric Hematopoietic Stem Cell Transplant Patients**

Christine S Higham , Alexis Melton, MD PhD , Sandhya Kharbanda, MD , Jasmeen Dara, MD ,  
Lena E. Winestone, MD , James N Huang, MD , Kristin A. Shimano, MD

- 25 patients at high risk for TMA enrolled
- High risk criteria –
  - Patients with high risk neuroblastoma, who were planned for tandem autologous HSCT with Cy/TT followed by CEM
  - Allo HSCT undergoing transplant with MAC and at least 3 of the following
    - Age > 10 years
    - Race other than Caucasian
    - Minor ABO incompatibility
    - Haplo HSCT

- Defibrotide – 6.25 mg/kg Q6H starting 1 day prior to conditioning till day +21
- Of 25 enrolled patients – 14 neuroblastoma, 11 allo
- Median age – 3.45 and 15.7 years in auto and allo respectively

- Overall incidence of TA-TMA – Only 1 patient developed (4%)
- Severe TA-TMA – None
  
- 3 patients required premature discontinuation of defibrotide due to bleeding
- The patient who developed TA-TMA had premature discontinuation of defibrotide on day+6

## ORIGINAL ARTICLE

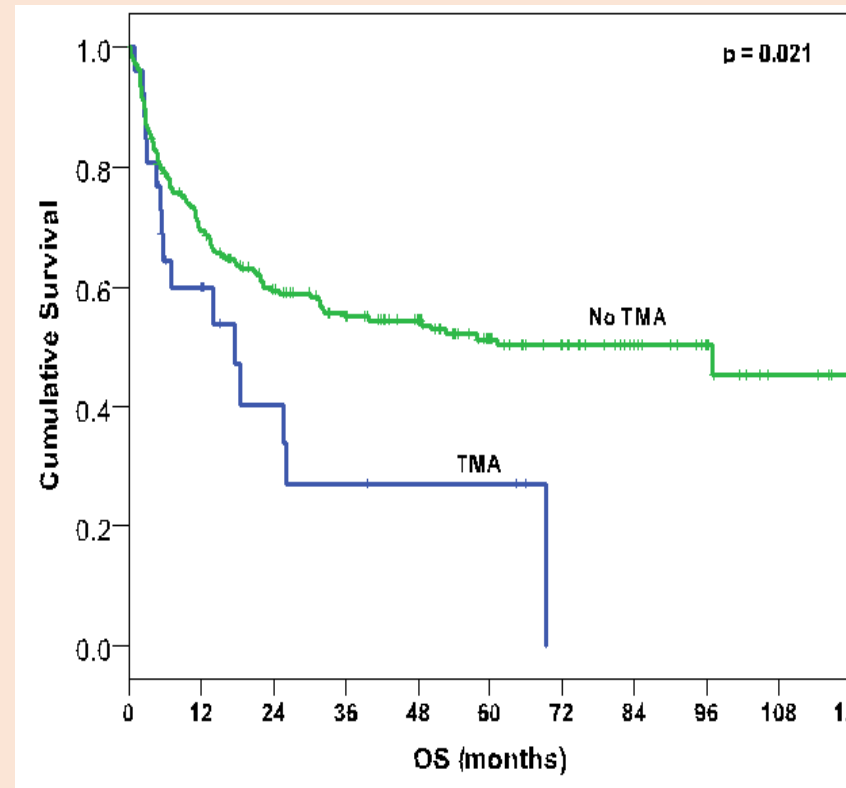
## Transplant-associated thrombotic microangiopathy is an endothelial complication associated with refractoriness of

Table 3. Lack of SEP as risk factor for TMA

	<i>TMA</i>		
	<i>HR</i>	<i>95% CI</i>	<i>P-values</i>
SEP yes vs no	0.23	0.11–0.49	< 0.001
Age per 10 years	1.27	0.994–1.06	0.095
Disease stage by EBMT score criteria 1–2 vs 0	1.70	0.79–3.67	0.173
Donor sex male vs female	0.50	0.26–0.93	0.030
Conditioning MAC+aplasia vs RIC	0.39	0.17–0.87	0.021
MMF yes vs no	2.34	1.10–5.14	0.027

# PROGNOSIS

- Uniformly shown to be associated with poorer survival compared to those who do not develop TMA



**Table 5. Poor prognostic factors in patients with TA-TMA**

- Proteinuria  $\geq 30$  mg/dL
- Elevated serum C5b-C9 levels
- Age  $\geq 18$  years
- Unrelated or haploidentical donors
- TMA index (LDH/platelets ratio)  $\geq 20$
- Schistocyte count  $> 5-10$ /hpf
- TMA without sirolimus exposure
- Elevated serum creatinine

Abbreviations: hpf = high-power field; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

# CONCLUSIONS

- TMA is a potentially life threatening complication post HSCT
- Epidemiology, risk factors, prognosis and treatment are not very clear.
- Type of transplant, use of CNIs, GVHD and infections are established risk factors for TA-TMA, not much is known of other risk factors that affect TA-TMA and its outcome

- New predictive and prognostic biomarkers help to better risk stratify patients and assess their prognosis more accurately
- Some of these biomarkers even help to guide treatment
- There is a plethora of new therapeutic drugs and prophylactic approaches, however most of these need further validation
- TMA has a strong adverse effect on survival

# SECTION 2 – VOD / SOS

# Introduction

- Also known as sinusoidal obstruction syndrome (SOS)
- Clinical syndrome after
  - high-dose chemotherapy
  - hematopoietic stem cell transplantation (HSCT)
  - high doses of radiotherapy
  - liver transplantation
- May be complicated by multiorgan disease (MOD) - ↑ mortality

# Introduction

- Incidence of post-transplant VOD/SOS: 5.3% - 13.7%
- Differs according to transplant settings and different studies
- Higher in pediatric high-risk population: 20 - 30%
- Early diagnosis and treatment correlated with ↑ survival

Kernan. Br J Haematol. 2018

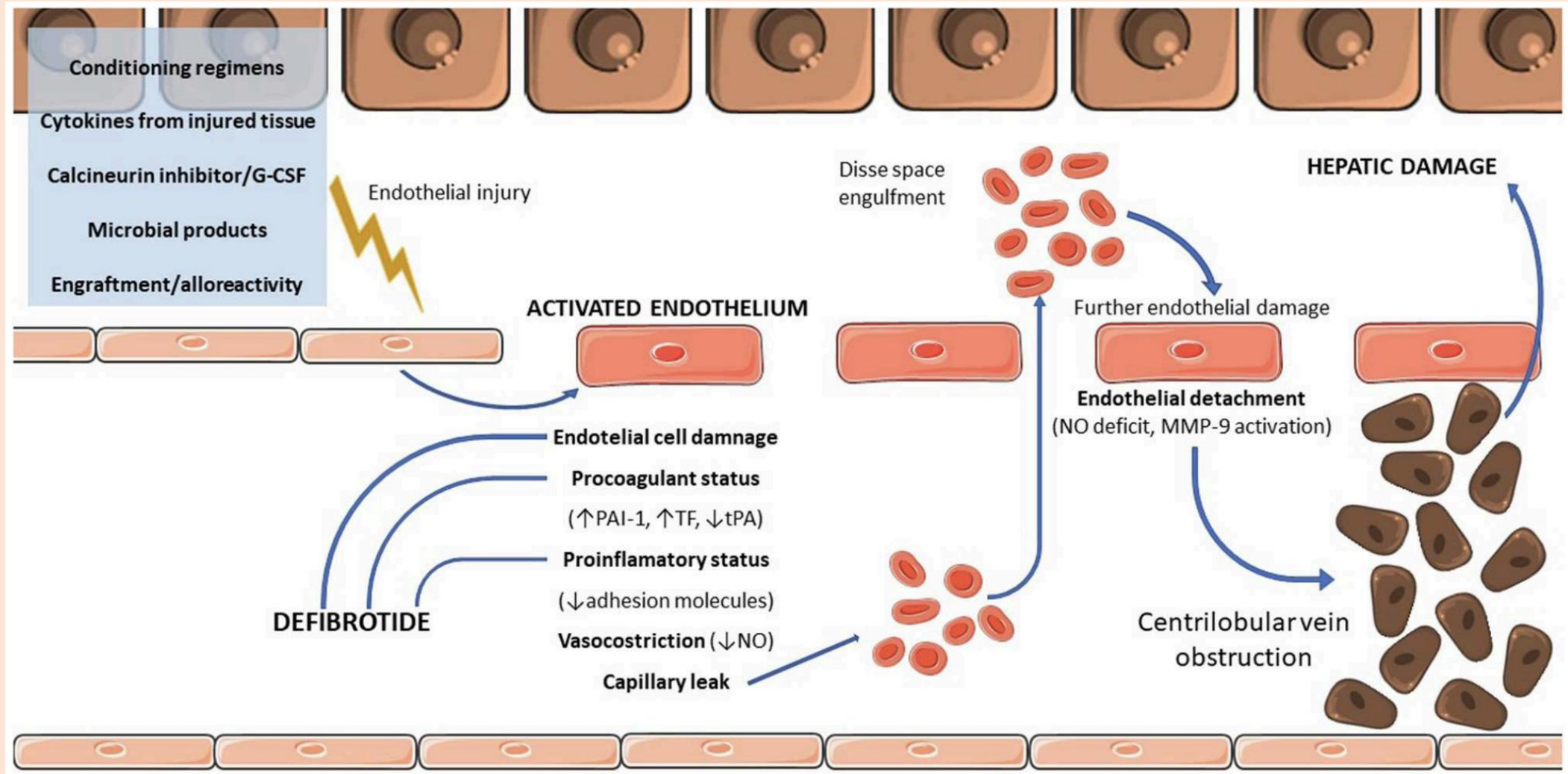
Carreras. Blood. 1999

Coppell JA. BBMT. 2010

Corbacioglu. BMT. 2018

Barker. BMT. 2003

# Pathophysiology



# Pathophysiology

- Blood flow obstruction:

  - Embolization of detached endothelial cells

  - proliferation of perisinusoidal stellate cells

  - proliferation of subendothelial fibroblasts

  - deposition of the extracellular matrix

  - peri-venular fibrosis

- Progressive obliteration --> hepatic congestion --> post-sinusoidal PH

# Pathophysiology

- Centrilobular regions: ↓ GSH --> ↑ sensitive to toxic agents
- GSH S-transferase M1 null genotype --> ↓ detoxifying capacity
- ↑ VOD/SOS in children: immature enzymatic system
- Nitric Oxide deficiency (post conditioning) → Endothelial detachment

# Risk factors

- Pre-transplantation patient characteristics
- Transplantation-related

# Pre-transplantation risk factors

<b>Risk factors</b>	<b>Odds Ratio</b>
Age	5.2-9.5
Increased transaminase levels	2.4-4.6
Pre-existing liver disease	3.4
Viral hepatitis	2
CMV positivity	3
Underlying disease/advanced malignancy	
Myelodysplasia	1.5
Inborn errors of metabolism	1.8
Leukemia	2.2
CML	3
Immunodeficiency	3.3
Thalassemia	4
Interval between diagnosis of malignancy and transplantation >12 months	2.3
Deteriorated health status within 30 days before transplantation	
Diarrhea	3.2
Fever	2.9

# Pre-transplantation risk factors

<b>Risk factors</b>	<b>Odds Ratio</b>
Parenteral nutrition before transplantation	3
Previous stem cell transplantation	1.9
Prior abdominal radiation	2.9
Prior treatment with gemtuzumab ozogamicin	19.8
Prior treatment with norethisterone	10.1
Poor Performance Status	3.1
GSTM1-null genotype	4.1
Impaired pulmonary function	2.4
Sepsis	4.1
Pretransplantation acyclovir	4.8
Ferritin levels >1000 ng/mL	3.1
Bilirubin >26 mmol/L before BMT	23.5

# Transplantation-related risk factors

Risk factors	Odds Ratio
Allogeneic versus autologous SCT	2.8
Sibling	2.8
Parental	4.6
Unrelated donor/HLA mismatch	1.4
Haploidentical	1.9
High-dose/myeloablative therapy	2.3-7.9
BU regimen versus others	2.6-4.5
BU + CY	3.9-5.1
Fludarabine	4
BCNU + CY + Etoposide	2.8
High-dose total body irradiation >12 Gy + CY	2.8
GVHD prophylaxis	
Sirolimus + methotrexate + tacrolimus	3
Methotrexate + cyclosporine	3.3
Cyclosporine	4.2
Non-T cell depleted grafts	2.2
Peripheral blood SCT versus BMT	1.3
Acute hepatic/gut GVHD	2

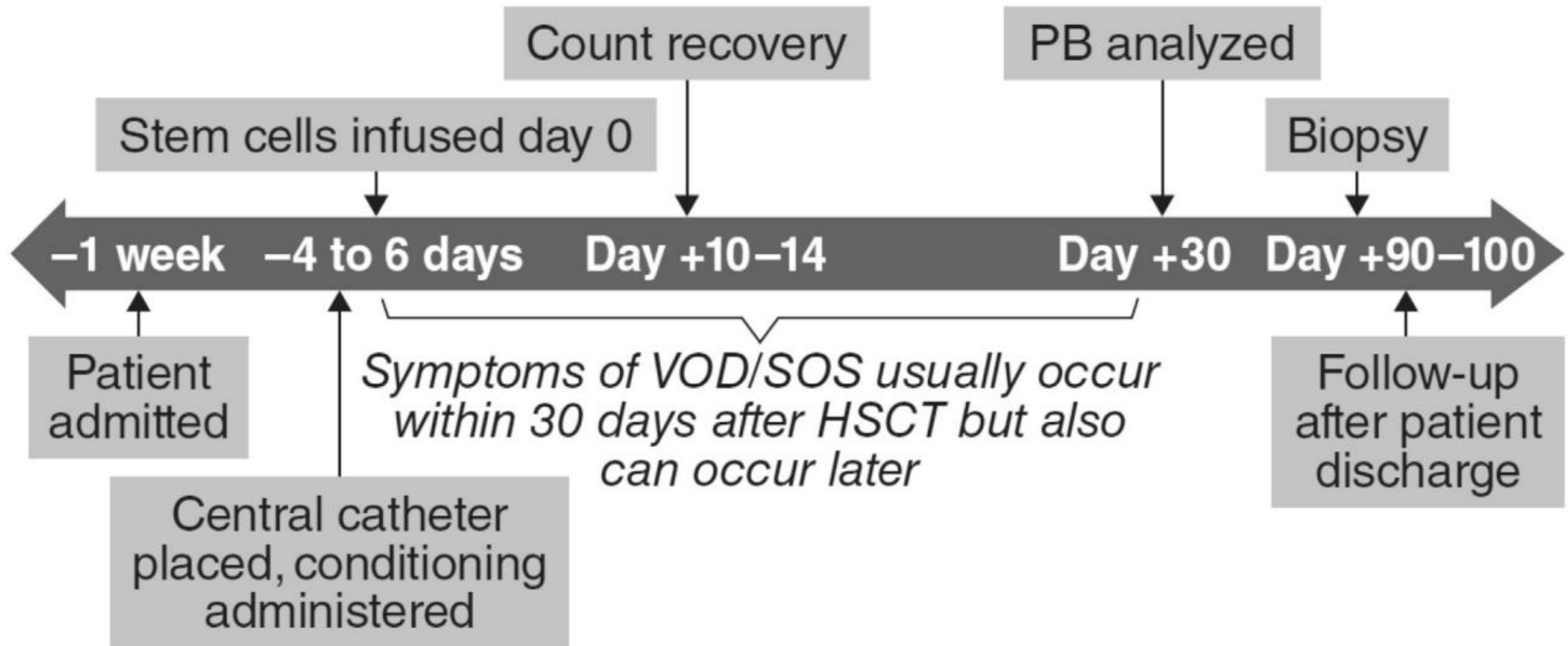
# Clinical presentation

- Rapid weight gain, unresponsive to diuretics
  - Hyperbilirubinemia
  - Tender hepatomegaly
  - Ascites
- 
- Occurs within 21 days after transplant
- 
- Late-onset VOD/SOS ---> recent entity (EBMT)

# Clinical presentation

- Onset of VOD/SOS – sudden or insidious
- Mild forms spontaneously resolving within few weeks
- Severe forms with organ damage and MOD (Lung/Kidney)
- MOD --> high mortality rate (>80%)

# Timing



# Differential diagnosis

- Fluid overload
- Drug-induced liver injury (DILI) or cholestasis
- Sepsis
- Infectious hepatitis
- Total parenteral nutrition
- Hepatic graft-versus-host disease (GvHD)

# Diagnostic Criteria

## (A) ADULTS

Modified Seattle criteria <sup>a</sup>	Baltimore criteria <sup>a</sup>	EBMT criteria <sup>a</sup>	
Presentation within 20 d from HSCT of $\geq 2$ of the following: <ul style="list-style-type: none"> <li>- Bilirubin <math>&gt; 2</math> mg/dL</li> <li>- Hepatomegaly, right-upper quadrant pain</li> <li>- Weight gain <math>&gt; 2\%</math> over baseline due to fluid retention</li> </ul>	Within 21 d from HSCT bilirubin $\geq 2$ mg/dL and at least 2 of the following: <ul style="list-style-type: none"> <li>- Painful hepatomegaly</li> <li>- Weight gain <math>&gt; 5\%</math></li> <li>- Ascites</li> </ul>	Classical VOD/SOS <sup>a</sup>  Within 21 d from HSCT bilirubin $\geq 2$ mg/dL and $\geq 2$ of the following: <ul style="list-style-type: none"> <li>- Painful hepatomegaly</li> <li>- Weight gain <math>&gt; 5\%</math></li> <li>- Ascites</li> </ul>	Late-onset VOD/SOS <sup>a</sup>  Classical SOS beyond day 21, OR Histologically proven SOS OR $\geq 2$ of the classical criteria AND ultrasound (US) or hemodynamic evidence of SOS

## (B) CHILDREN

No time onset limitation for SOS/VOD occurrence

The presence of  $\geq 2$  of the following parameters<sup>b</sup>:

- Unexplained refractoriness to platelets transfusions defined as  $\geq 1$  weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines.<sup>c</sup>
- Otherwise unexplained weight gain on 3 consecutive days despite the use of diuretics or a weight gain  $> 5\%$  above baseline value
- Hepatomegaly (best if confirmed by imaging such as US, CT or MRI) above baseline value measured pre-HSCT
- Ascites (best if confirmed by imaging such as US, CT or MRI) above baseline value measured pre-HSCT
- Increase of bilirubin above baseline value on 3 consecutive days or bilirubin  $\geq 2$  mg/dL within 72 h

# Severity – EBMT (2023)

	<b>Mild<sup>a</sup></b>	<b>Moderate<sup>a</sup></b>	<b>Severe</b>	<b>Very severe – MOD<sup>b</sup></b>
Time since clinical symptoms of SOS/VOD	>7 days	5–7 days	≤4 days	Any time
Bilirubin (mg/dl)	≥2 and <3	≥3 and <5	≥5 and <8	≥8
Bilirubin kinetic			Doubling within 48 h	
Transaminases	≤2 × normal	>2 and ≤5 × normal	>5 and ≤8 × normal	>8 × normal
Weight increase			≥5%	≥10%
Renal function (creatininemia)	Baseline at transplant	<1.5 × baseline at transplant	≥1.5 and <2 × baseline at transplant	≥2 × baseline at transplant or diagnosis of MOD <sup>b</sup>

# Imaging

- Ultrasonography + Doppler

Assessment of both parenchymal and vascular changes

Signs of portal hypertension

However, operator dependent

- MR / CT: Logistical issues in critically ill patients

# Other investigations

- Liver biopsy

Potential complications in thrombocytopenic patients

Cannot be considered routine practice

- Measurement of HVPG

> 10mm Hg - Hallmark of portal hypertension

Invasive procedure

# Other investigations

- Transient Elastography

Liver stiffness measurement (LSM)

Non-invasive

LSM ↑ before clinical VOD/SOS diagnosis

Limitations: Operator training / Massive ascites / BMI > 30

# Treatment

- Supportive and Intensive Care
  
- Defibrotide

# Supportive and Intensive Care

- Daily monitoring:

Jaundice

Hepatomegaly

Fluid overload and weight gain

Ascites

# Supportive and Intensive Care

- Therapeutic measures to reduce the discomfort:

Massive ascites - Paracentesis

Pleural effusion - Thoracentesis

Hypoxia - Oxygen therapy

Pain - Analgesics

Renal failure - Hemo-dialysis

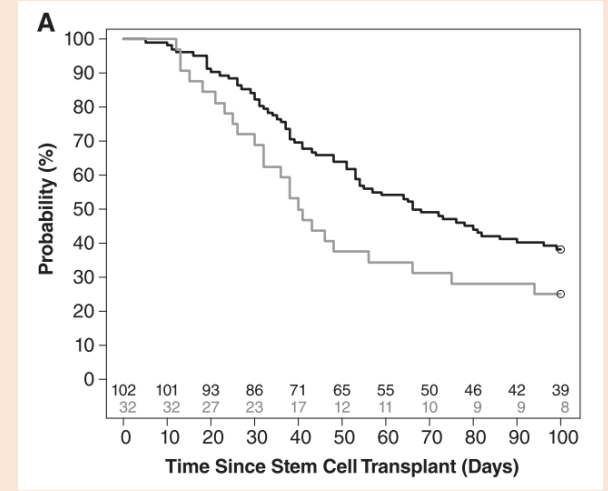
# Defibrotide

- Only registered drug for moderate to severe VOD/SOS
- Derived from porcine intestinal mucosa
- Mixture of polydeoxyribonucleotide (mainly single-stranded)
- Interact with fibroblast growth factors
- Exert fibrogenic and angiogenic effects
- Leading to endothelial stabilization

## CLINICAL TRIALS AND OBSERVATIONS

### Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure

Paul G. Richardson,<sup>1</sup> Marcie L. Riches,<sup>2</sup> Nancy A. Kernan,<sup>3</sup> Joel A. Brochstein,<sup>4</sup> Shin Mineishi,<sup>5</sup> Amanda M. Termuhlen,<sup>6</sup> Sally Arai,<sup>7</sup> Stephan A. Grupp,<sup>8</sup> Eva C. Guinan,<sup>1,9</sup> Paul L. Martin,<sup>10</sup> Gideon Steinbach,<sup>11</sup> Amrita Krishnan,<sup>12</sup> Eneida R. Nemecek,<sup>13</sup> Sergio Giralt,<sup>14</sup> Tulio Rodriguez,<sup>15</sup> Reggie Duerst,<sup>16</sup> John Doyle,<sup>17</sup> Joseph H. Antin,<sup>1</sup> Angela Smith,<sup>18</sup> Leslie Lehmann,<sup>1,9</sup> Richard Champlin,<sup>19</sup> Alfred Gillio,<sup>20</sup> Rajinder Bajwa,<sup>21</sup> Ralph B. D'Agostino Sr,<sup>22</sup> Joseph Massaro,<sup>22</sup> Diane Warren,<sup>1</sup> Maja Miloslavsky,<sup>23</sup> Robin L. Hume,<sup>24</sup> Massimo Iacobelli,<sup>25</sup> Bijan Nejadnik,<sup>26</sup> Alison L. Hannah,<sup>27</sup> and Robert J. Soiffer<sup>1</sup>



- Historically controlled multicenter open-label phase III study
- From 1995 to 2008
- Prospectively enrolled patients with established hepatic VOD/SOS
- Defibrotide 25 mg/kg/day (prospective) vs placebo cohort (retrospective)



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## Biology of Blood and Marrow Transplantation

journal homepage: [www.bbmt.org](http://www.bbmt.org)

ASBMT™

American Society for Blood and Marrow Transplantation

Clinical Research: Supportive Care

### Defibrotide for the Treatment of Hepatic Veno-Occlusive Disease: Final Results From the International Compassionate-Use Program



Selim Corbacioglu <sup>1,\*</sup>, Enric Carreras <sup>2</sup>, Mohamad Mohty <sup>3,4,5</sup>, Antonio Pagliuca <sup>6</sup>, Jaap Jan Boelens <sup>7,8</sup>, Gandhi Damaj <sup>9</sup>, Massimo Iacobelli <sup>10,†</sup>, Dietger Niederwieser <sup>11</sup>, Eduardo Olavarria <sup>12</sup>, Felipe Suarez <sup>13</sup>, Tapani Ruutu <sup>14</sup>, Leo Verdonck <sup>15</sup>, Robin Hume <sup>16</sup>, Bijan Nejadnik <sup>16,‡</sup>, Chinglin Lai <sup>16,‡</sup>, Giorgia Finetto <sup>17,§</sup>, Paul Richardson <sup>18</sup>

- Defibrotide doses ranged from 10mg to 80mg/kg (no specific protocol)
- 689 of 710 patients developed VOD/SOS after HSCT
- 499 after an allogeneic HSCT, and 112 after autologous HSCT
- 100-day survival was 54% (overall)



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# Biology of Blood and Marrow Transplantation

journal homepage: [www.bbmt.org](http://www.bbmt.org)



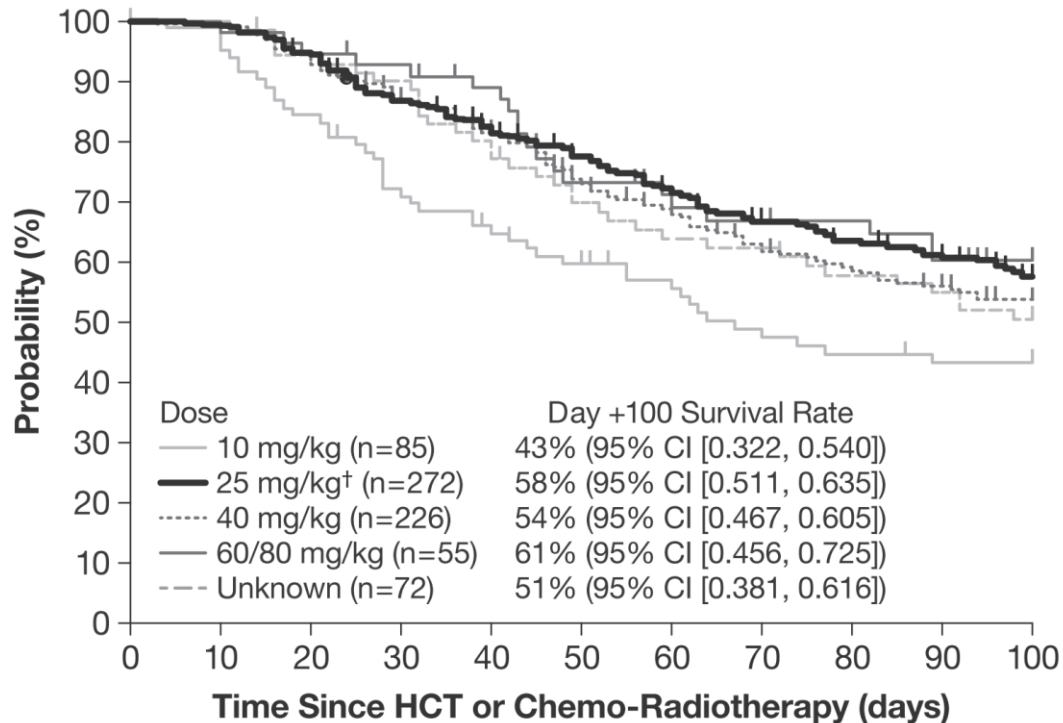
ASBMT  
American Society for Blood and Marrow Transplantation

Clinical Research: Supportive Care

## Defibrotide for the Treatment of Hepatic Veno-Occlusive Disease: Final Results From the International Compassionate-Use Program



Selim Corbacioglu <sup>1,\*</sup>, Enric Carreras <sup>2</sup>, Mohamad Mohty <sup>3,4,5</sup>, Antonio Pagliuca <sup>6</sup>, Jaap Jan Boelens <sup>7,8</sup>, Gandhi Damaj <sup>9</sup>, Massimo Iacobelli <sup>10,†</sup>, Dietger Niederwieser <sup>11</sup>, Eduardo Olavarria <sup>12</sup>, Felipe Suarez <sup>13</sup>, Tapani Ruutu <sup>14</sup>, Leo Verdonck <sup>15</sup>, Robin Hume <sup>16</sup>, Bijan Nejadnik <sup>16,‡</sup>, Chinglin Lai <sup>16,‡</sup>, Giorgia Finetto <sup>17,§</sup>, Paul Richardson <sup>18</sup>



### Exposure to Defibrotide in Patients with Dosing Data

Dose (mg/kg/day)	Age <18 yr n = 267*	Age ≥18 yr n = 371*	Total Population N = 638 <sup>†</sup>
10	22 (8)	63 (17)	85 (13)
25 <sup>‡</sup>	131 (49)	141 (38)	272 (43)
40	78 (29)	148 (40)	226 (35)
60/80	36 (13)	19 (5)	55 (9)

**Final results from a defibrotide treatment-IND study for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome**

- Prospective open-label, single-arm study in an expanded access program
- Dose of 25 mg/kg for at least 21 days
- 1,000 patients with VOD/SOS after HSCT
- 85% allogeneic HSCT and 15% autologous HSCT

**Final results from a defibrotide treatment-IND study for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome**

- 100-day OS was 58.9% (overall)
  - 68.5% (VOD/SOS without MOD)
  - 49.5% (with MOD)
- Earlier initiation of defibrotide treatment was significantly associated with higher day +100 survival ( $P < 0.001$ )

**Final results from a defibrotide treatment-IND study for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome**

- Most important TRAEs:
  - pulmonary hemorrhage (4.6%)
  - gastrointestinal hemorrhage (3%)
  - epistaxis (2.3%)
  - hypotension (2%)

# Other therapies – limited benefit / data

- N-Acetyl Cysteine
- Tissue Plasminogen Activator

# Prophylaxis for VOD

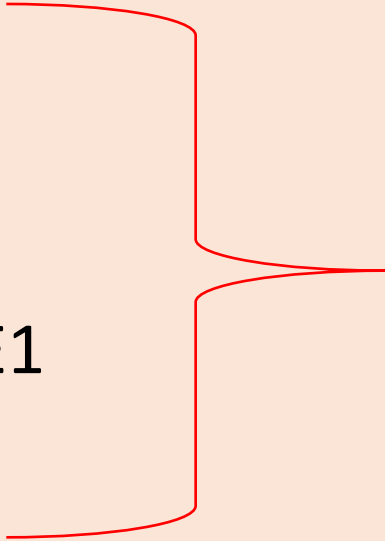
- Urso-deoxy Cholic Acid (UDCA)

- Heparin

- Antithrombin

- Prostaglandin E1

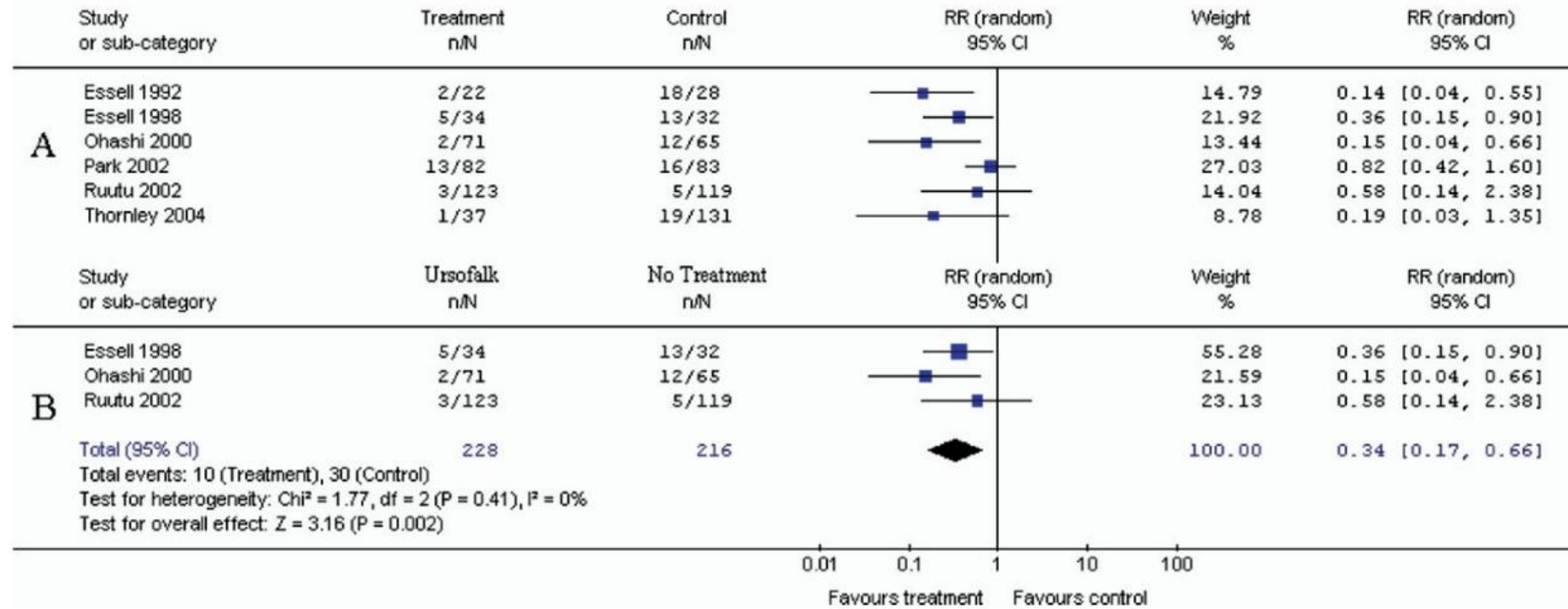
- Pentoxifylline



Little / No Efficacy

## 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<sup>1</sup>, Alan Timmouth, Dean Fergusson, Lothar Huebsch, David S Allan



**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.

# Key Takeaways

- Diagnosis is based mainly on clinical criteria
- Biomarkers are not yet validated
- Most reliable imaging method is USG + Doppler
- Differential diagnosis is quite challenging
- More than one complication can occur simultaneously in same patient

# Key Takeaways

- Invasive diagnostic methods hard to be widely used in critically ill
- Elastometry deserves further validation by prospective studies
- Earlier mortality rates of VOD + MOD: > 80%
- Nowadays: 100-day mortality: 22% (5-year mortality: 35%)
- Decreased mortality attributed to better supportive care, MDT, risk stratification, and earlier treatment

# Before we close

- Q1 – Which of the following is not a 3<sup>rd</sup> hit for development of TMA
  - Cyclosporine
  - Acute GVHD
  - Conditioning therapy
  - Sepsis

- Q2 – Which of the following statement about management of HVOD is correct
  - Defibrotide dose below 25 mg/kg/day is not effective
  - Gastrointestinal bleeding is an important complication of defibrotide
  - Narsoplimab is the novel standard of care for HVOD
  - In the absence of specific treatment, HVOD does not resolve

**THANK YOU**