Critical early complications of HSCT: management and treatment of Veno-Occlusive Disease

Worldwide Network for Blood & Marrow Transplantation (WBMT)

Satellite Symposium organised and funded by
Jazz Pharmaceuticals in collaboration with
WBMT

Welcome

Yoshihisa Kodera

Chairmen:

Hildegard Greinix

Nicolas Novitzky

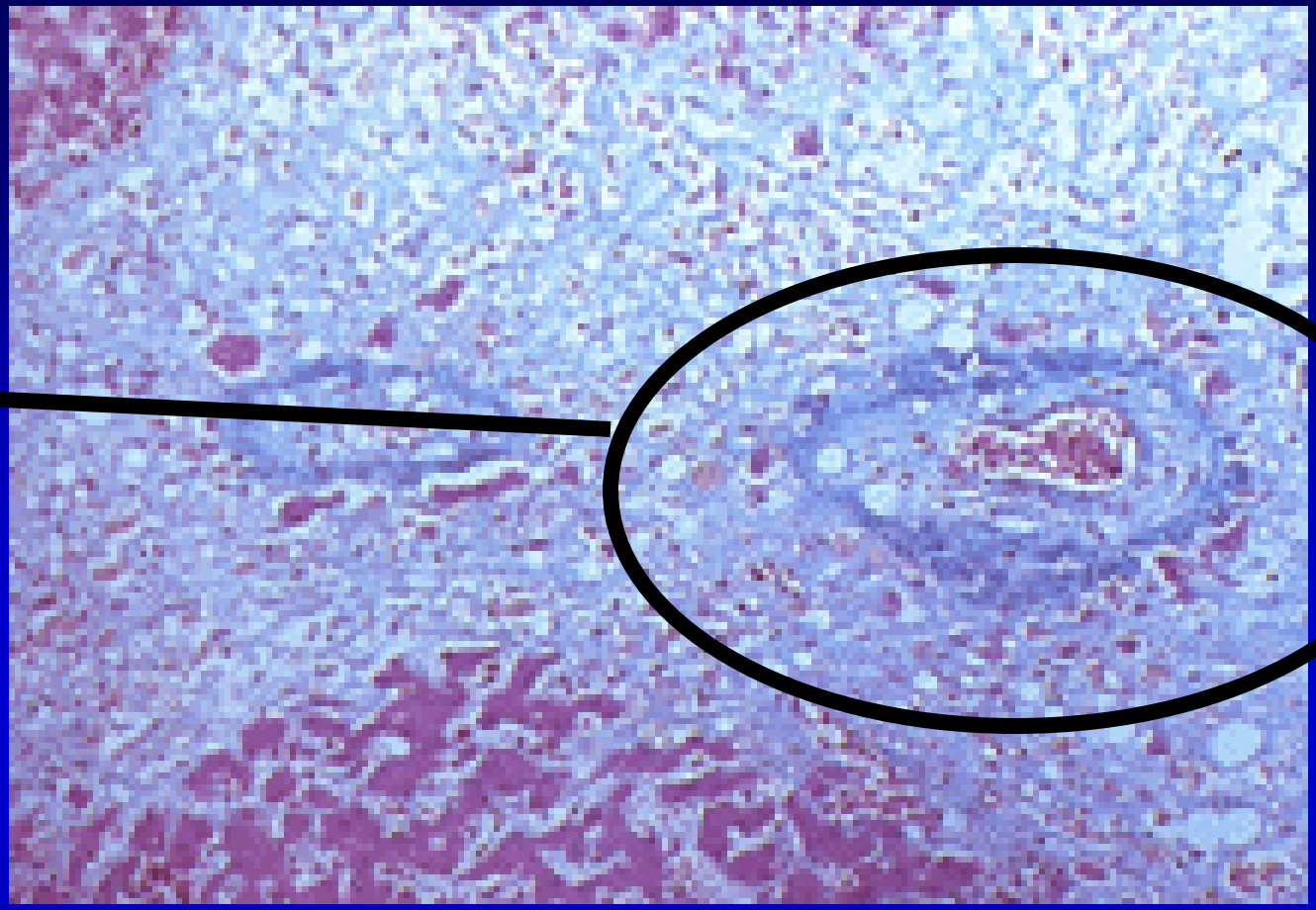
Mahmoud Aljurf

Pathophysiology and management of VOD, including a case study

Dietger Niederwieser

Universität Leipzig

Occlusion of Hepatic Venules



After HSCT:

- 45% mild-moderate VOD and 25% severe VOD ; occlusion of hepatic venules not seen at path ~ should the syndrome be renamed ?
- "Sinusoidal Obstruction Syndrome" [SOS] (vs VOD)

- Current Consensus: VOD (SOS)

Shulman, et al. Hepatology 1994; 19: 1779.

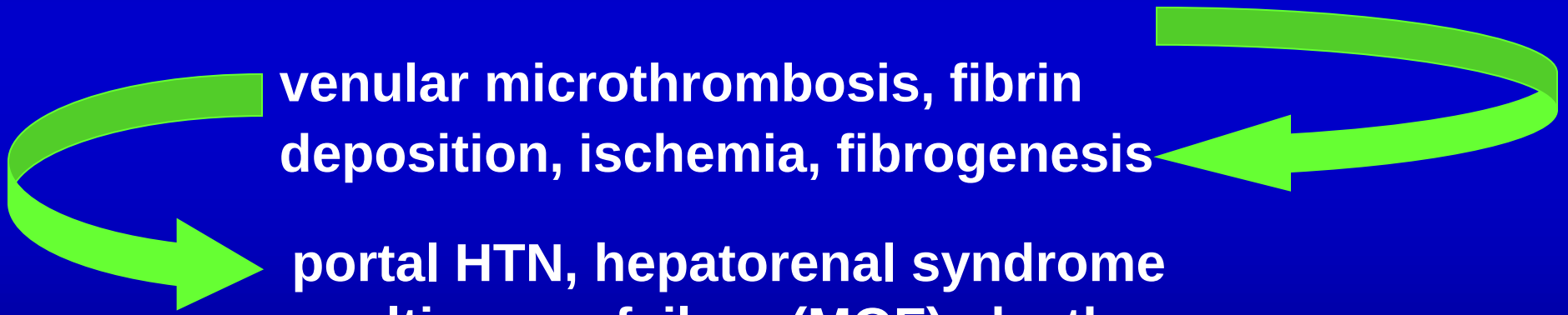
Deleve et al. Clin Sem Liver Dz. 2002

Kumar et al, Mayo Clinic Proc. 2006

Hepatic VOD/SOS post SCT

Pathophysiology:

Primary injury to sinusoidal endothelial cells (SEC), hepatocytes, stellate cells

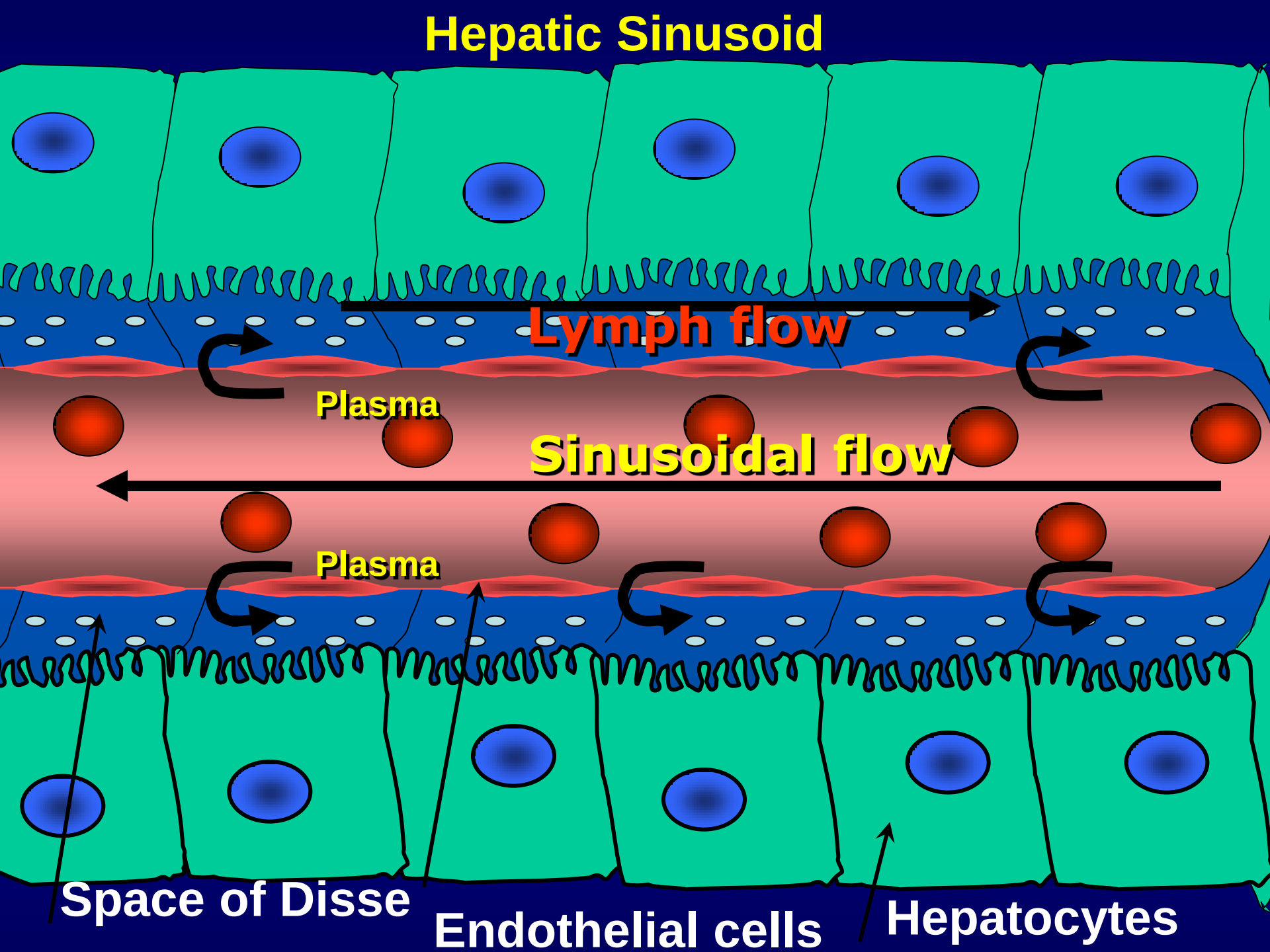


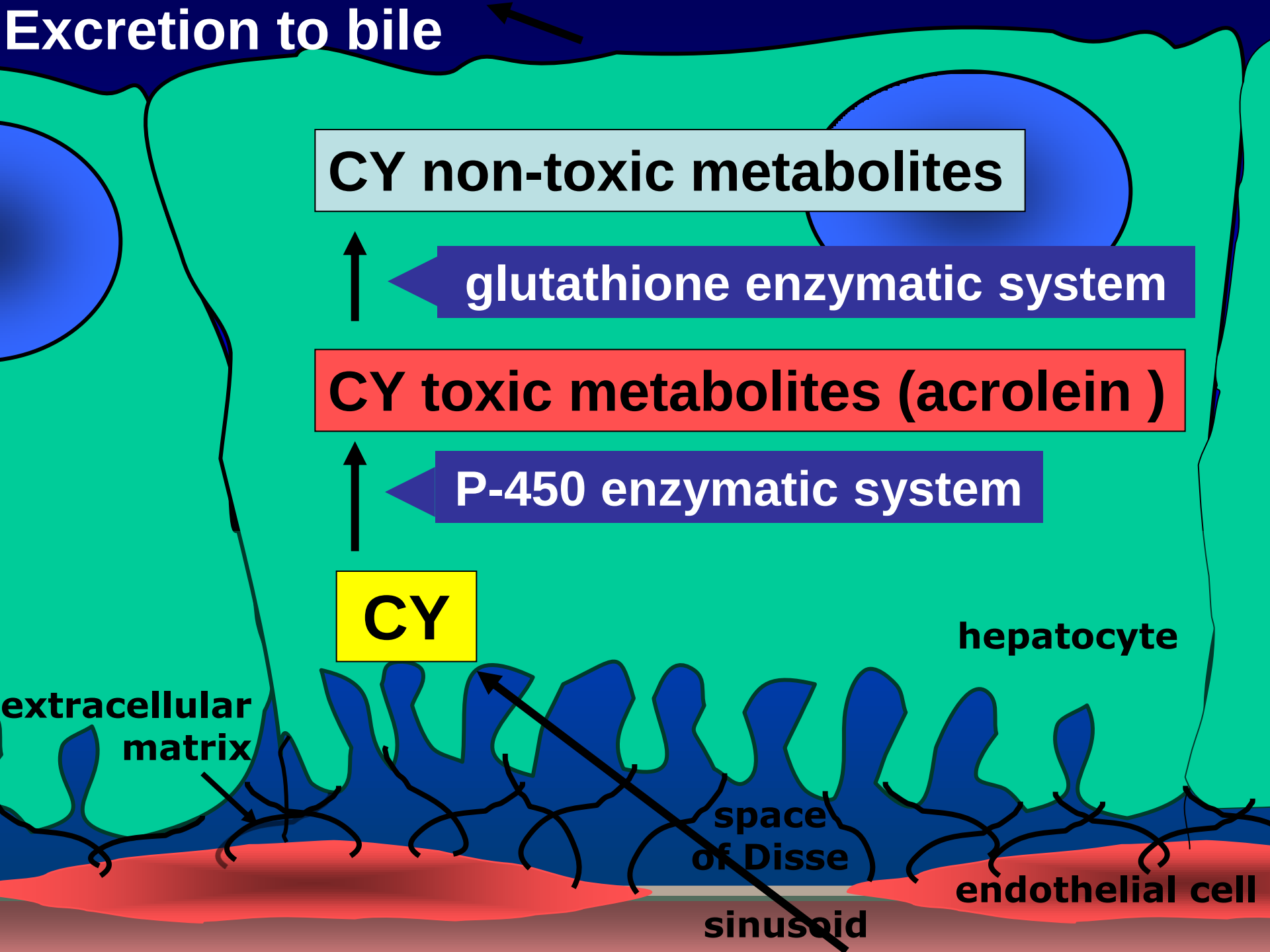
Richardson & Guinan BJH 1999; Ho et al , BMT 2008

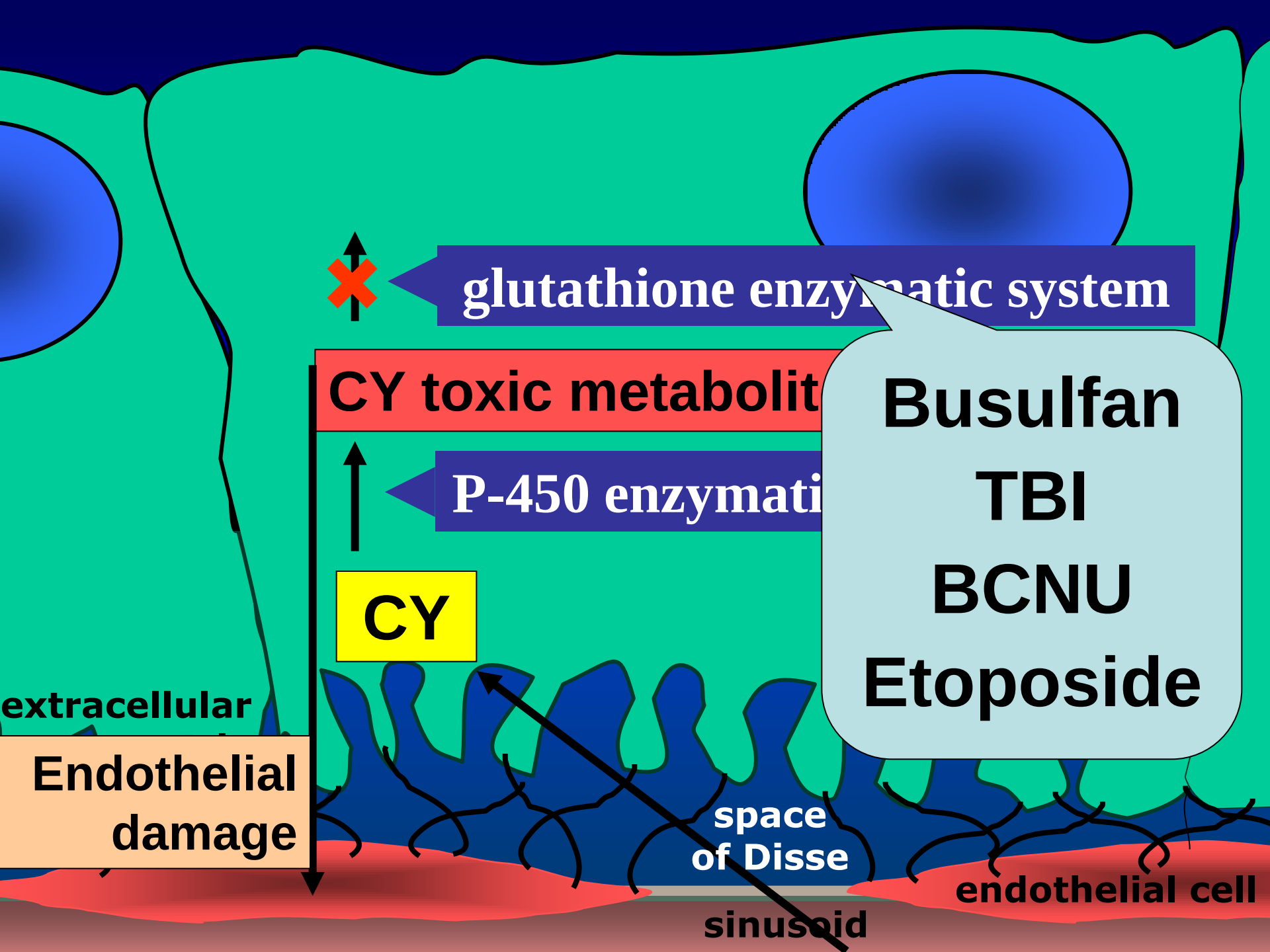
Diagnostic criteria for VOD

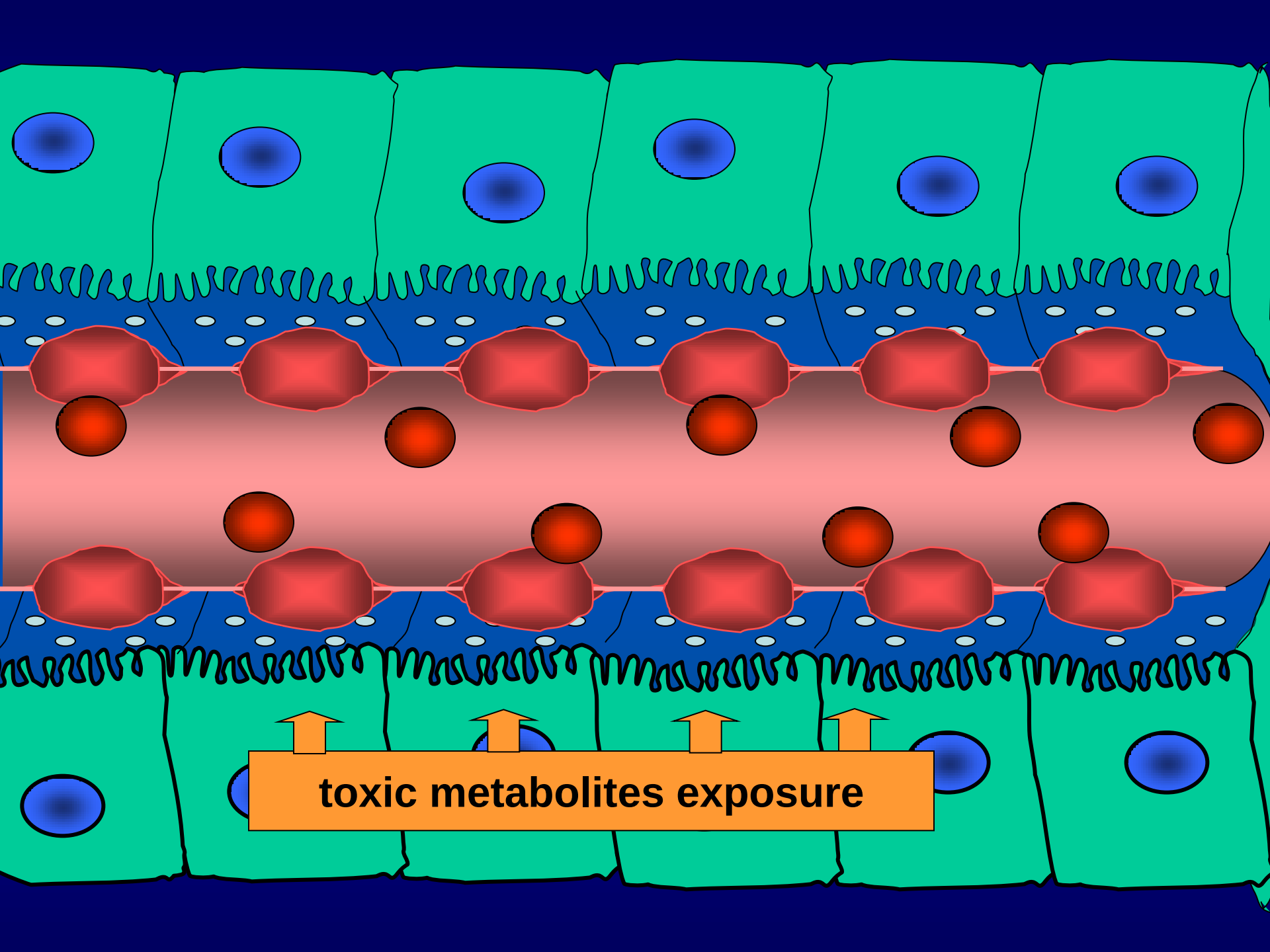
Baltimore Criteria	Seattle Criteria
Hyperbilirubinaemia ≥ 2 mg /dl before day 21 after SCT and at least two of the following: ▪ Hepatomegaly (usually painful) ▪ Ascites ▪ Weight gain >5% from baseline	Presence before day 20 after SCT of two or more of the following: ▪ Bilirubin ≥ 2 mg /dl ▪ Hepatomegaly, right upper quadrant pain ▪ Ascites ± unexplained weight gain of >2% baseline
Modified Baltimore Criteria	
As above, before day 35 after SCT.	

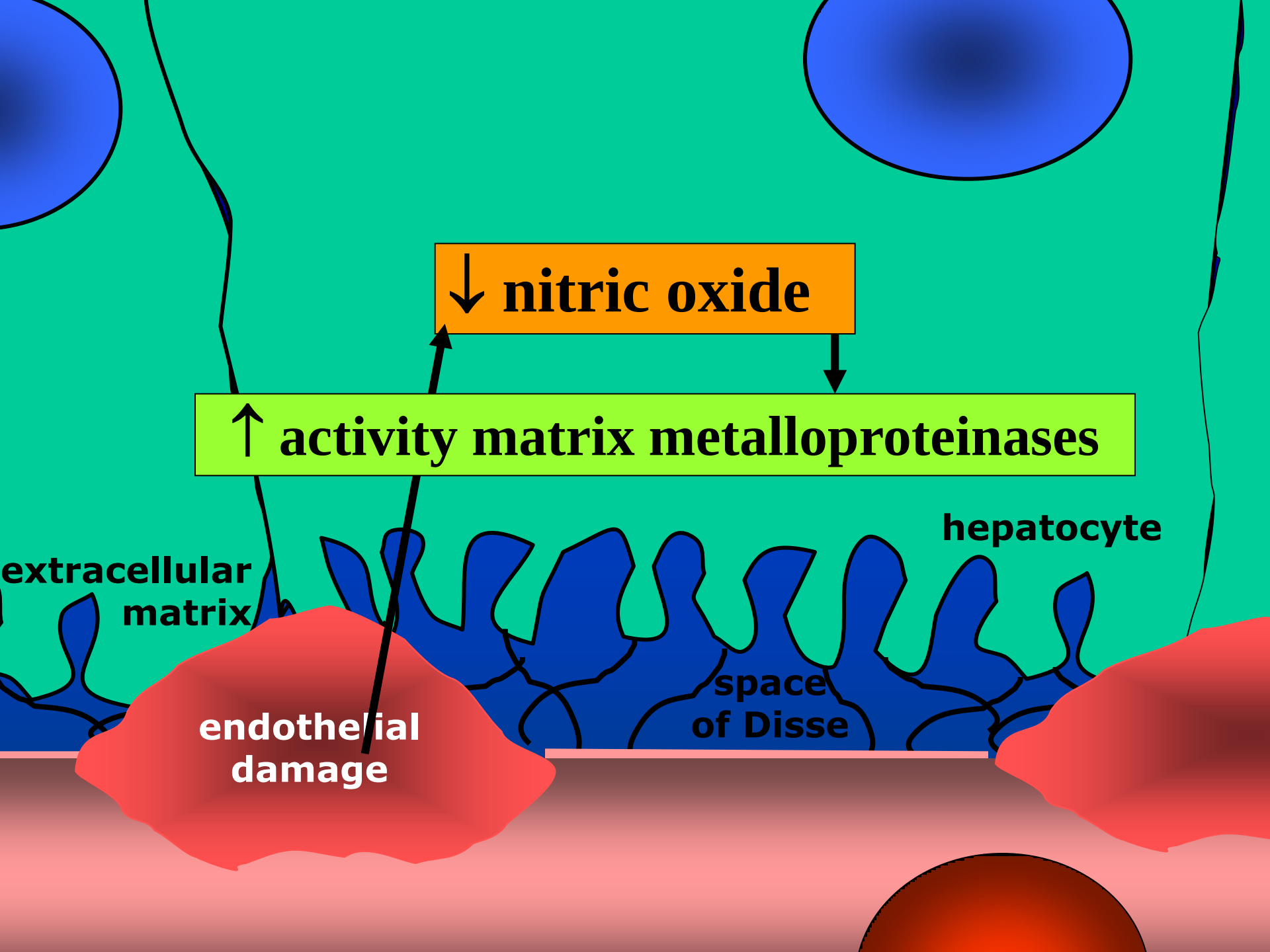
Severe VOD when:
Baltimore criteria for VOD (21 days after SCT) with MOF, as defined as: ▪ Renal or, ▪ Respiratory (ARDS) or, ▪ CNS dysfunction

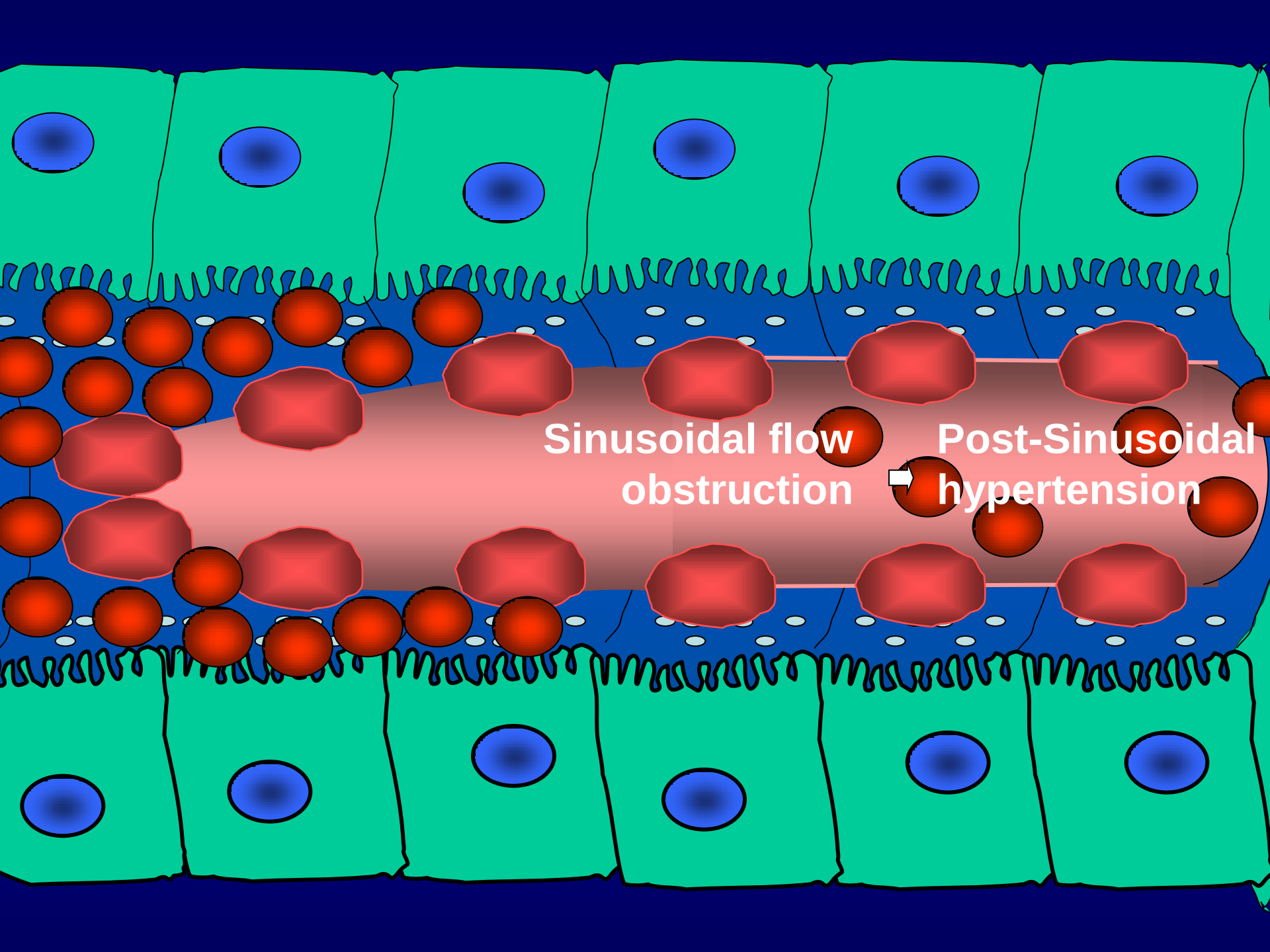

Hepatic Sinusoid
Lymph flow
Plasma
Sinusoidal flow
Plasma
Space of Disse
Endothelial cells
Hepatocytes

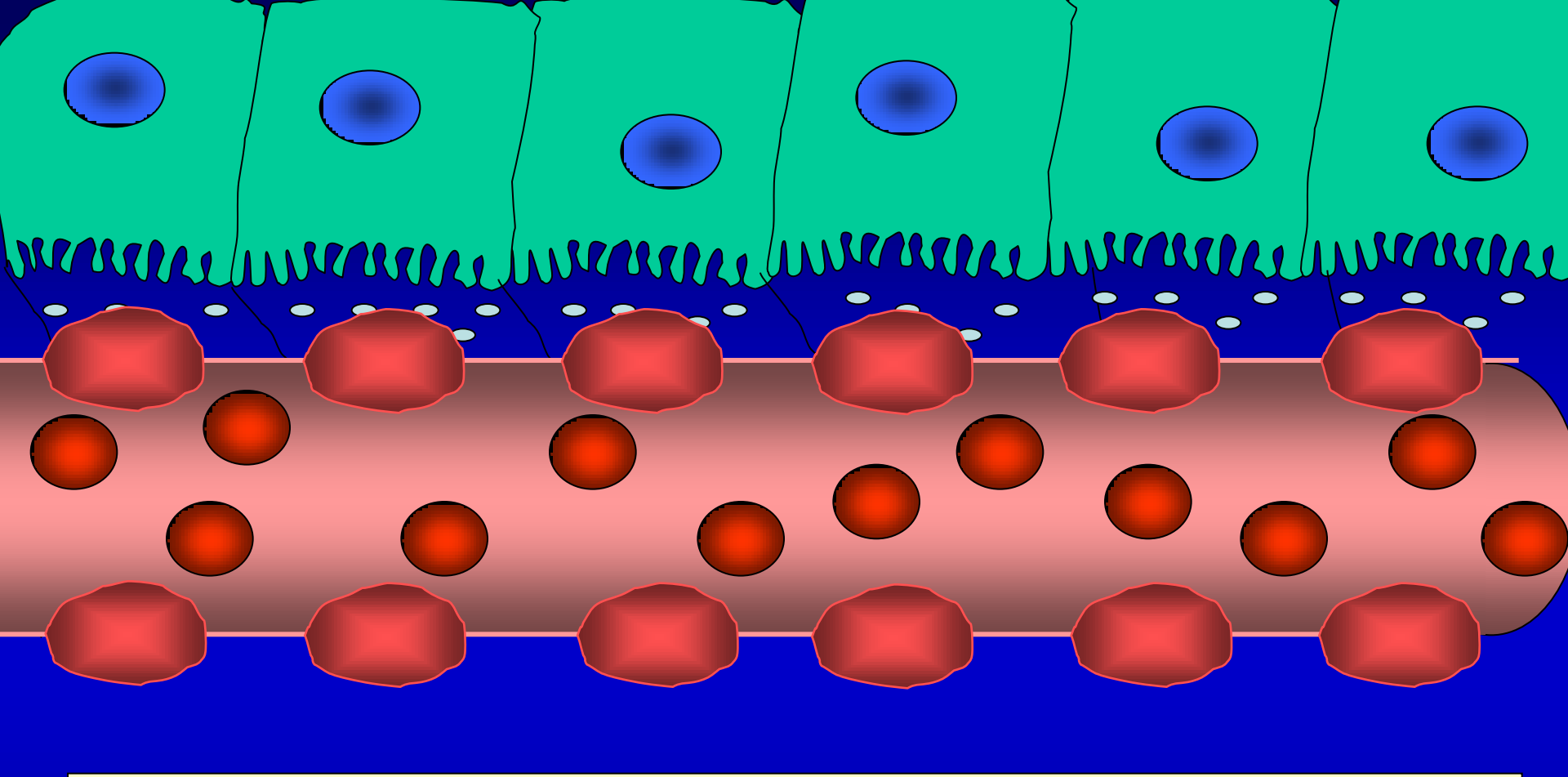

Excretion to bile
CY non-toxic metabolites
glutathione enzymatic system
CY toxic metabolites (acrolein)
P-450 enzymatic system
CY
hepatocyte
extracellular matrix
space of Disse
endothelial cell
sinusoid


glutathione enzymatic system
CY toxic metabolit
P-450 enzymati
CY
Busulfan
TBI
BCNU
Etoposide
extracellular
Endothelial damage
space of Disse
endothelial cell
sinusoid


toxic metabolites exposure

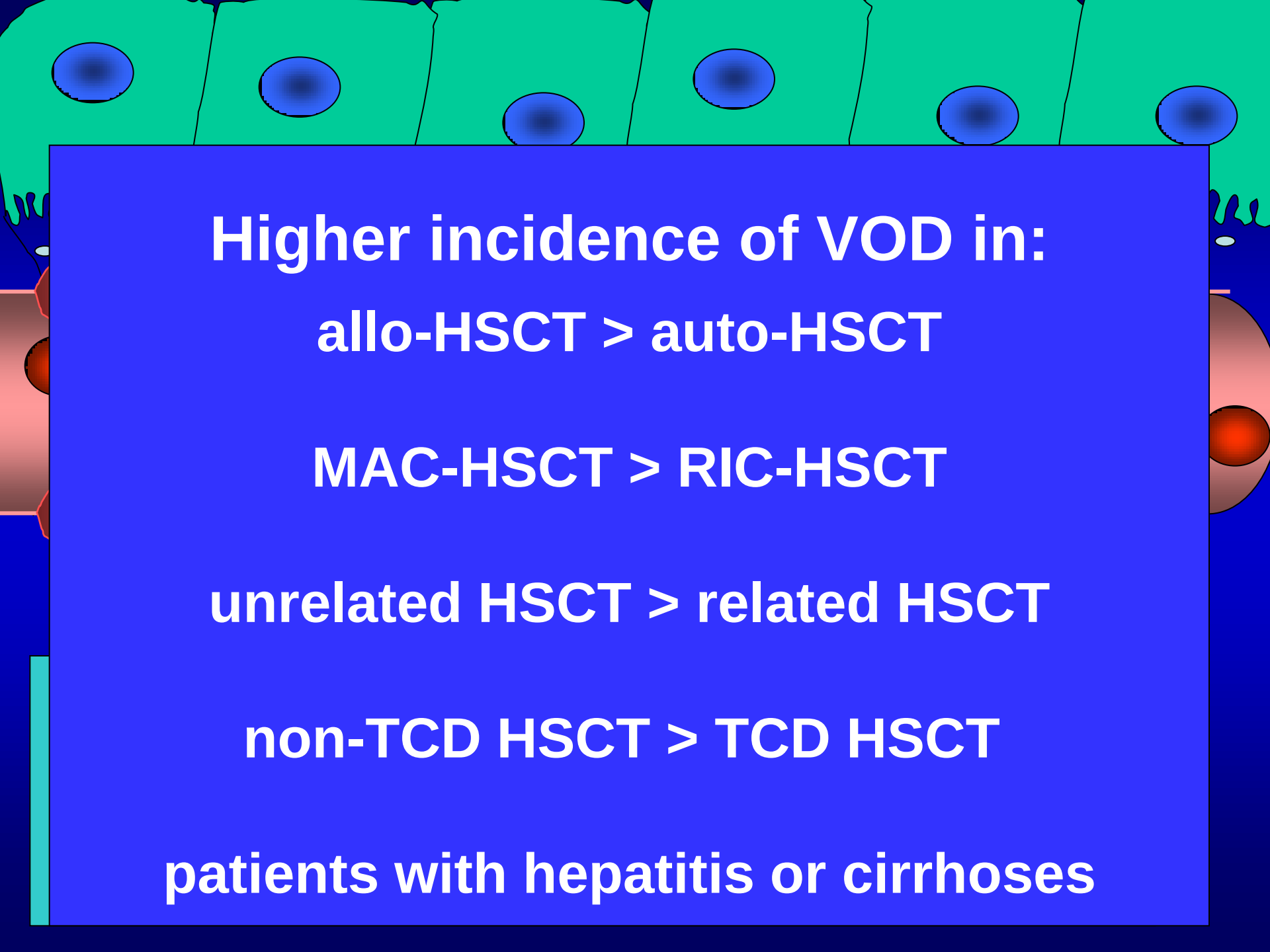

↓ nitric oxide
↑ activity matrix metalloproteinases
hepatocyte
extracellular matrix
space of Disse
endothelial damage


Sinusoidal flow obstruction
Post-Sinusoidal hypertension



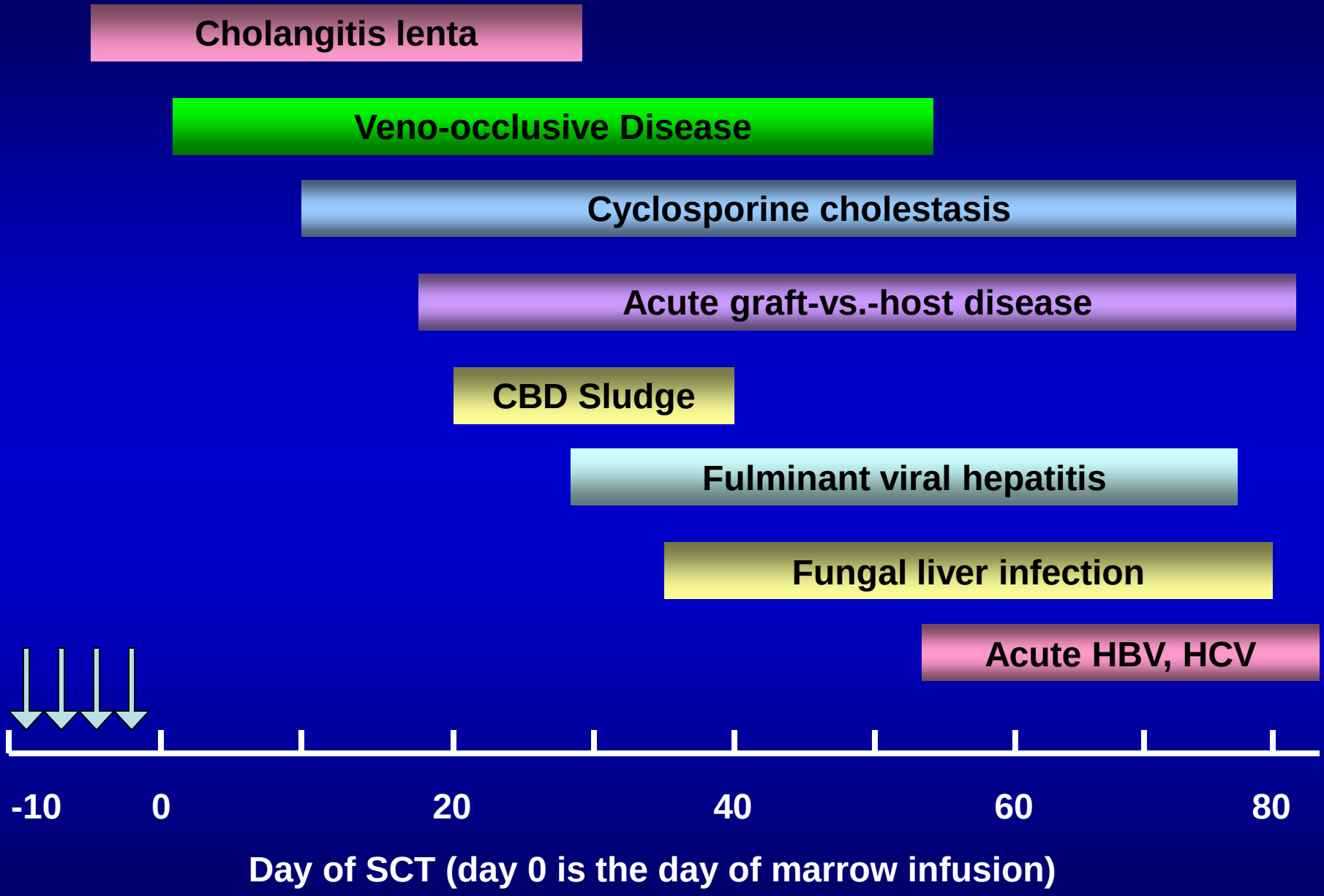
↑ Willebrand factor and thrombomodulin
↑ protein fragments 1+2 and thrombin-antithrombin
↑ proc
↑ thro
↓ natu

Endothelial injury → procoagulant status
→ FVIII/vWF deposition perivenular zone


Higher incidence of VOD in:
allo-HSCT > auto-HSCT
MAC-HSCT > RIC-HSCT
unrelated HSCT > related HSCT
non-TCD HSCT > TCD HSCT
patients with hepatitis or cirrhoses

Differential Diagnosis

Rapid Weight Gain	Hepatomegaly	Jaundice
VOD	VOD	VOD
CHF	CHF	Sepsis
Renal Failure	Tumor	GVHD
Sepsis	EBV	Cyclosporin
	Budd-Chiari	Hemolysis


Cholangitis lenta
Veno-occlusive Disease
Cyclosporine cholestasis
Acute graft-vs.-host disease
CBD Sludge
Fulminant viral hepatitis
Fungal liver infection
Acute HBV, HCV
-10
0
20
40
60
80
Day of SCT (day 0 is the day of marrow infusion)

Laboratory Results in VOD

High	Low
Bilirubin *	Platelets *
AST/ALT *	Protein C
Thrombopoietin	Antithrombin III
PAI-1 *	TNFα
Collagen propeptide *	
Hyaluronic acid *	
Tenascin, TIMP-1	

* More important investigation

Diagnostic criteria for VOD

- Transjugular liver biopsy and measurement of hepatic vein pressure
  - Bleeding risk
- Liverbiopsy
  - Extremly high bleeding risk

Ultrasound and CT in VOD

- Useful in identifying:
  - hepatomegaly, ascites, attenuated hepatic vein diameter and flow, portal vein thrombosis
  - Doppler ultrasound findings, late in VOD:
    - reversal of portal flow, increased resistive index to hepatic arterial flow
- Useful in excluding:
  - pericardial effusion, constrictive pericarditis
  - hepatic vein obstruction, mass lesions in the liver

Hepatic Veno-Occlusive Disease

Definition

- Rare and potentially fatal complication of BMT/SCT
- Other cancer therapies can cause VOD

Statistics

- Approximately, 45,000 patients in US & EU received blood and bone marrow transplants in 2002
  - Approximately 12-15% BMT/SCT patients develop hepatic VOD
    - Up to 1/3 progress to Severe VOD with MOF
      - ~80% of patients with Severe VOD die within 100 days

Treatment

- No therapy currently licensed for VOD prophylaxis
- Defibrotide is licensed for the treatment of severe VOD following HSCT in the EU

J. A. Coppell et al. *Biol Blood Marrow Transplant 16:157-168, 2010*

VOD incidence in 135 publications

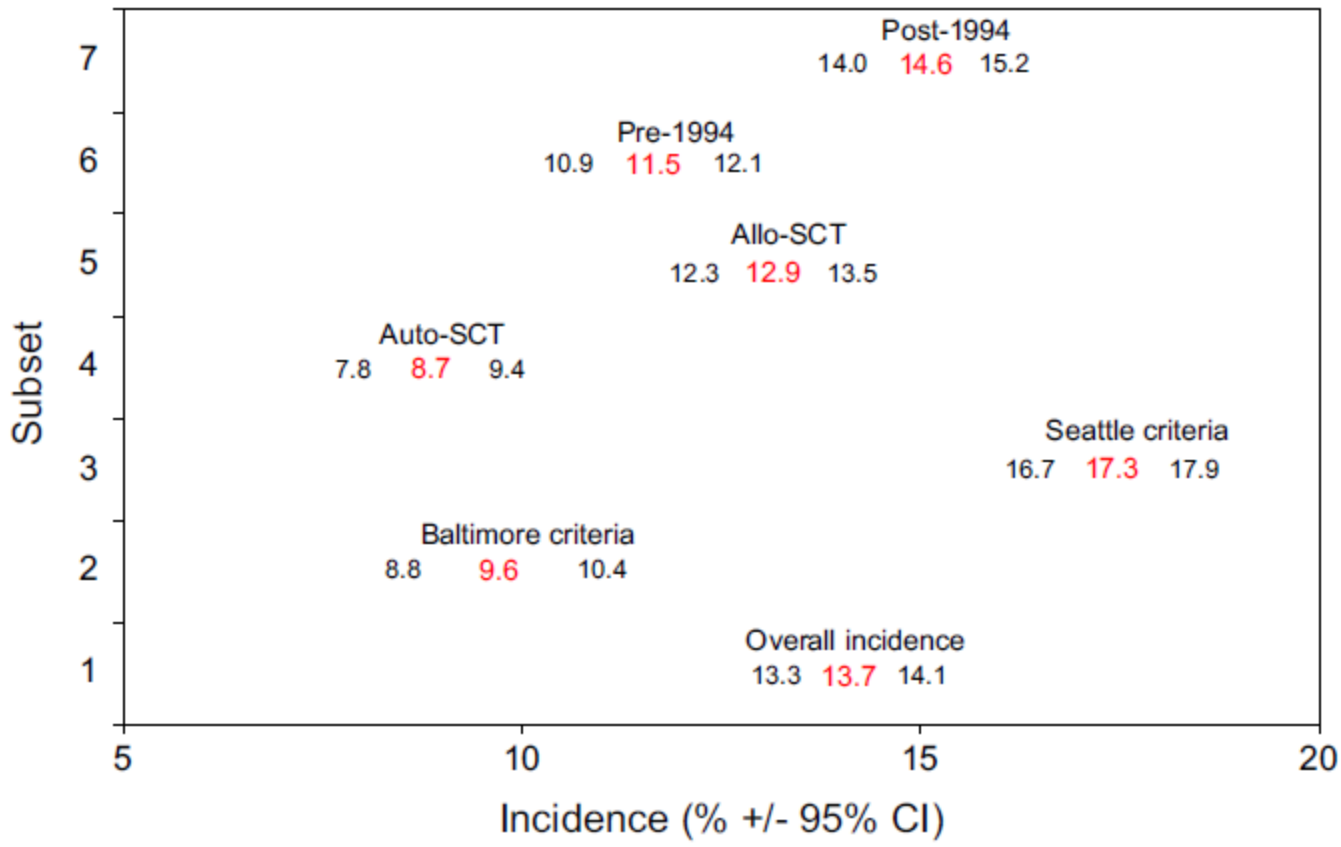


Figure 1. Graphical representation of the data presented in Table 1.

J. A. Coppell et al.

Biol Blood Marrow Transplant 16:157-168, 2010

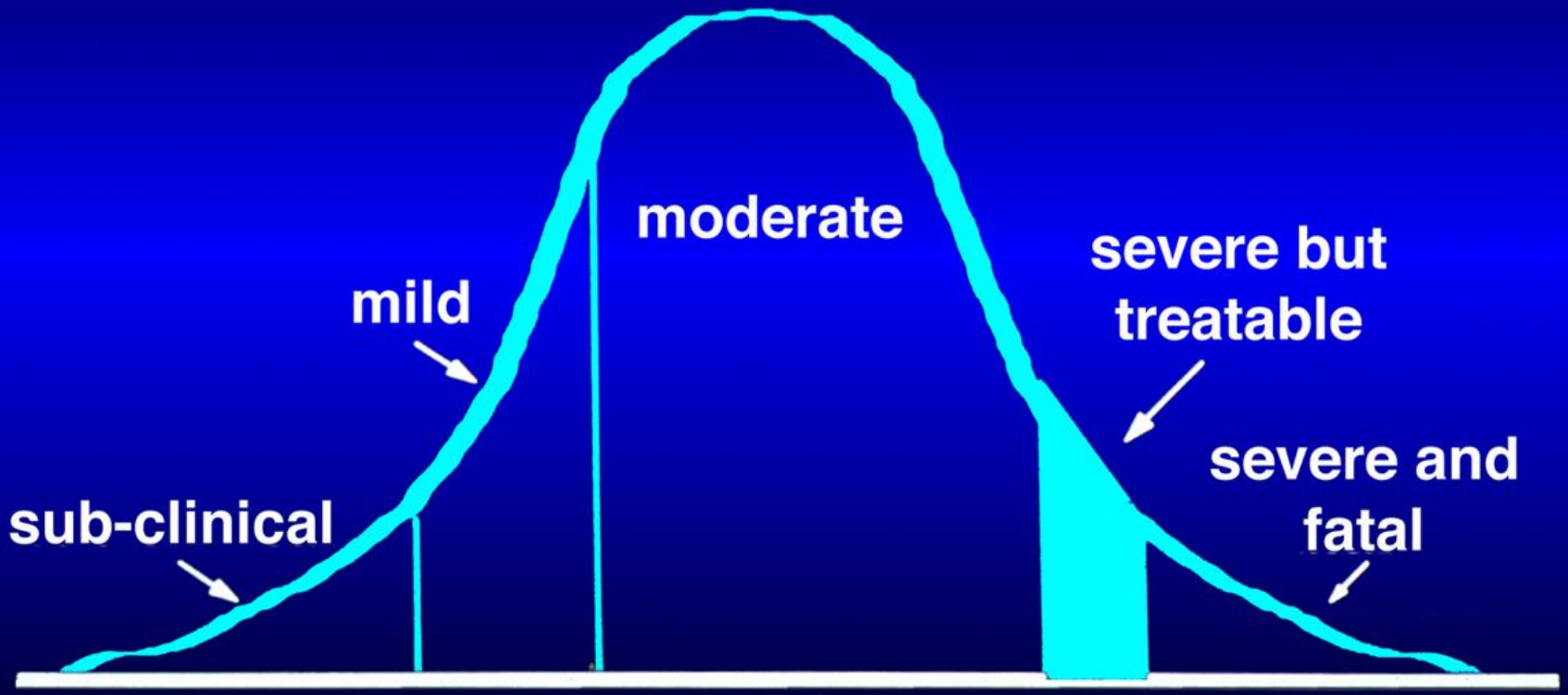
Incidence and outcome of Hepatic VOD after SCT: A prospective cohort study of the EBMT

- N= 1652, 73 centers
- Jaundice; > 5% wt. gain; ascites; painful hepatomegaly
- Incidence of VOD: n=83 (5%)
- Severe VOD: n=23 (28%)
- Allo >> auto
- Heparin (UFH) not effective as prophylaxis

- All cause D+100 mortality was 100% in pts with severe VOD

Carreras et al, Blood 1998

The clinical spectrum of VOD



Clinical features of SCT patients with VOD according to severity of disease (n=355)

	Mild (n=44)	Moderate (n=92)	Severe (n=54)
Day +100 mortality (all cause) (%)	4 (9%)	21 (23%)	53 (89%)
Weight gain before Day +20, kg (% increase)	3.9 (7.0%)	5.9 (10.1%)	9.1 (15.5%)
Maximum total serum bilirubin before Day +20 (mg/dL)	4.7	7.9	26.0
Patients with peripheral edema (%)	10 (23%)	64 (70%)	46 (85%)
Patients with ascites (%)	2 (5%)	15 (16%)	26 (48%)

McDonald GB et al. *Ann Intern Med* 1993;118:255–267

Prognosis of VOD (SOS)

- **Most useful:**
  - **rate of rise of bilirubin**
  - **rate of wt gain**
  - **MOF:**
    - **oxygen requirement**
    - **renal dysfunction**
    - **encephalopathy**

} **Bearman Model**

- **Severe VOD**
  - **All cause mortality > 80%**
  - **Current standard: best supportive care**
  - **Defibrotide is licensed for the treatment of severe VOD following HSCT in the EU**

McDonald et al, Ann Int Med,1993; Bearman et al, JCO, 1993; Haire et al, JAMA, 1995; Carreras et al, Blood, 1998; Wadleigh et al, Curr Op in Hematology, 2003; Pihusch et al, Transplantation, 2005; Cesaro et. al, Haematologica, 2005; Bulley et. al, Ped Blood Cancer, 2006; Cheuk et. al, BMT, 2007; Coppel et al, EBMT 2008

Overall Survival of patients with severe VOD

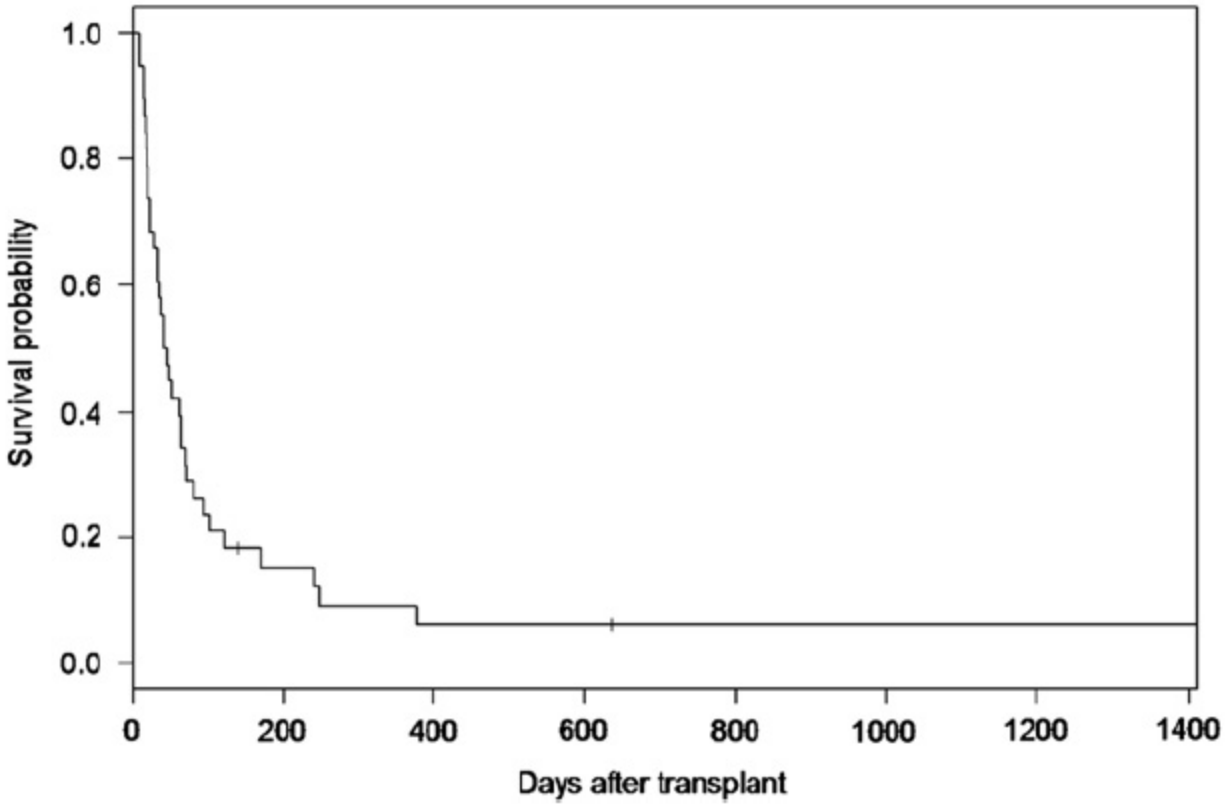
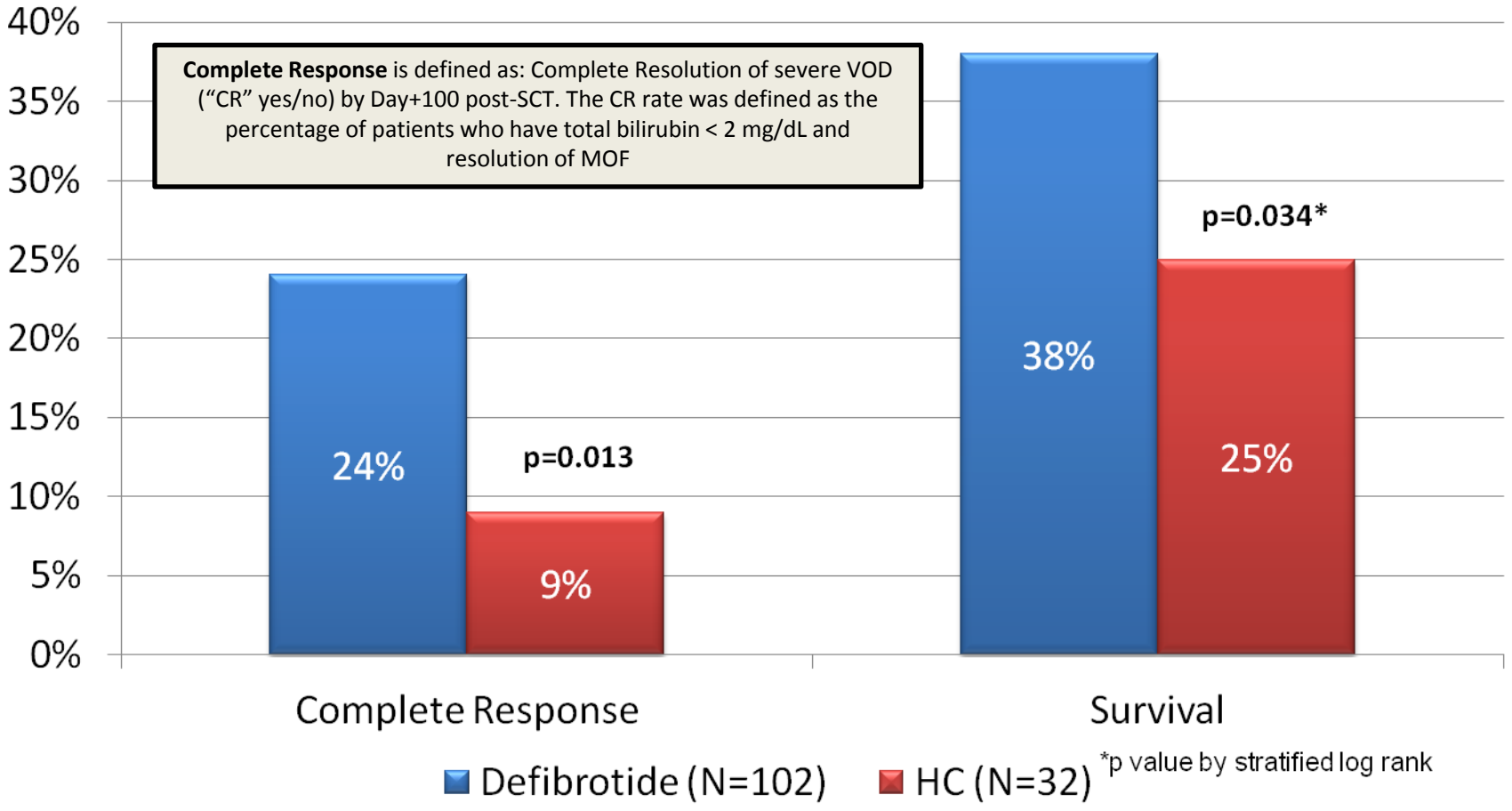


Figure 2. Kaplan-Meier survival curve for retrospective historical controls with severe VOD (MOF) (n = 38).

J. A. Coppell et al.

Biol Blood Marrow Transplant 16:157-168, 2010

In sVOD with MOF Defibrotide increases Complete Response and reduces Mortality at Day 100 post-SCT



Richardson P et al. *Blood (ASH Annual Meeting Abstracts)* 2009;114:654

Case study (male 35 years)

- Diagnosis:
  - Polytransfused myelodysplastic syndrome (RAEB)
  - COPD

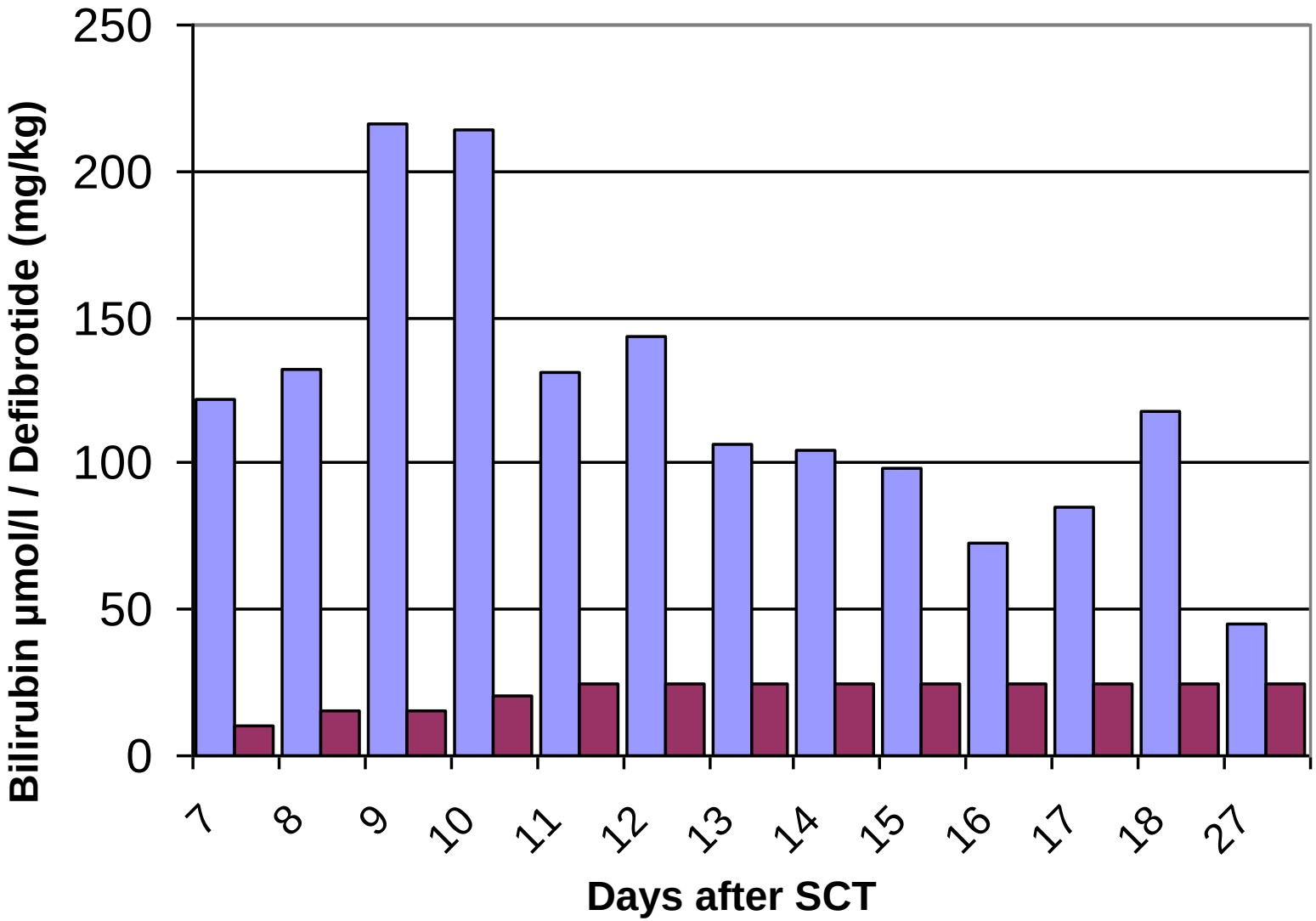
  - matched MUD; BG-difference (A Rh-neg. -> A Rh-pos.)
  - Conditioning therapy: Busulfan 16mg/kg, Cyclophosphamide 2 x 60 mg/kg and ATG 3 x 15 mg/kg
  - Day +8 hepatosplenomegaly and pain right upper quadrant
  - Fluid retention with weight gain of 5 kg

- On examination:
  - Jaundice, liver 4 cm MCL and spleen 2 cm enlarged
  - Mucositis grade 1
  - Sonography: spleen 17x7 cm, portal vein 17 mm, no pericardial effusion

Case study (male 35 years) II diagnosis VOD

Days after SCT	**+4**	**+5**	**+6**	**+7**
ALAT	0,54	0,39	0,32	0,29
ASAT	0,35	0,23	0,24	0,24
AP	5,1	5,5	7,0	7,1
Bili	**78,7**	**104**	**100,3**	**122**
Dir.		75	72,2	98.2
Indir.			28,1	24,2
LDH	4,07	3,99	3,66	3,57
Haptoglobin		0,8		
Hb (g/dl)	12,1	11,8	12	11,0
Thr	21	24	18	11
Krea-Clear	62			76
CRP	31,2	51	43	40

Case study (male 35 years) III
VOD and defribotide



Conclusions/Future directions

VOD/SOS ~

- Definition of severity – MOF
- Prevention of VOD a priority ~ a uniformly successful approach remains to be defined
- Treatment of sVOD ~ new therapies are urgently needed
- DF shows promise in severe VOD/MOF
- Specific at risk populations identified (prior mylotarg, sirolimus use)
- Development of endothelial, imaging data as diagnostic & prognostic tools ongoing
- Genetic risk, pharmacogenomic studies under consideration
- Novel trial designs to support new drug evaluation in process

Hepatic Veno-Occlusive Disease: Special Patient Risks

Mahmoud Aljurf

HEPATIC VENO-OCCLUSIVE DISEASE SPECIAL RISK PATIENTS

Mahmoud Aljurf, MD

King Faisal Specialist Hospital and Research Centre

Riyadh, Saudi Arabia

Africa, Middle East and certain parts of Asia and Latin America have special risk groups for hepatic Veno-occlusive Disease (VOD)

High Prevalence

- Hemoglobinopathies
- Congenital bone marrow failure syndromes
- Acquired Severe Aplastic Anemia
- Other high risk groups for tissue damaged by chemotherapy
- Gene polymorphism for MTHFR (possibly other enzymes)

Hemoglobinopathies

- Micro vascular damage (Sickle cell and possibly others)
- Iron overload with poor iron chelation
- Hepatitis B & C infection

Bone Marrow Failure

- Heavily pre-transfused with iron load
- Hepatitis B & C infection
- Seronegative Hepatitis Aplasia syndrome

Infectious factors contributing to liver disease in Africa, Middle East and certain parts of Asia

- Hepatitis B infection
- Hepatitis C infection
- Schistosomiasis
- Enterohemorrhagic fevers ?

Protection from Hepatic Toxicity

- Iron Chelation pre HSCT
- IV Busulfan
- Methotrexate dose
- Careful observation and management of Hepatic VOD

HSCT and VOD in South Africa

Nicolas Novitzky

UCT

SINUSOIDAL OBSTRUCTION SYNDROME
THE SASCeTS DATABASE

Nicolas Novitzky PhD, FCP(SA)

Registry review

UCT

SASCeTS

Patient Population

Variable	Value
Total transplants	683
Reporting centres	4
Age, median	45.9
Female / male	290 / 393
Alive / dead / missing	459 / 115 / 107
All allo / first allogeneic / autologous	312 / 252 / 354
Conditioning in allogeneic SCT Myeloablative / RIC /missing	268 / 37 / 7
Donor type: sibling / MUD	230/ 82
Stem cell source BM / PBPC / CBB	7 / 270 / 7

SASCeTS Database

VOD

Patient Population

Variable	No
All patients	683
VOD	8 (1%)
Race: • Caucasaian: • Mixed race: • Asian: • African:	 4 1 2 1
Diagnosis: • AML • ALL • MF • NHL • Myeloma: • Fanconi	 3 1 1 1 1 1
Stem cell source • Allogeneic / autologous • MUD / Sibling	 6 / 2 3 / 3
Karnofsky @ SCT	95%

SASCeTS Database

VOD

Patient Population

Variable	No
Conditioning Myeloablative / RIC	7 / 1
Conditioning: TBI Busulfan + other Busulfex + other Melphalan	 1 4 2 1
GvHD prophylaxis TcD	 6
VOD prophylaxis None: Heparin:	 3 5
Conditioning Myeloablative / RIC	6 / 1

Outcomes

VOD

Patient Population

Variable	No
Engraftment yes / no	8 / 0
GvHD 1-II: IIII:	4 3 1
VOD Moderate MOF	 4 4
Died / Alive	3 /5

Summary of the results

VOD

Capsule

Variable	Value
Patients	8
Caucasian	3
Myeloablative	7
GvHD	4
Dead / alive	3 / 5

HSCT and VOD in Nigeria

Nosa Bazuaye

Veno-occlusive Disease (Sinusoidal Obstruction Syndrome) following Haematopoietic Stem Cell Transplantation: The Nigerian experience

presented at the
WBMT/WHO 2014 workshop on Hematopoietic stem cell transplantation Cape town South Africa

Dr Bazuaye GN
Associate Professor of Hematology and Blood Transfusion
University of Benin Teaching Hospital
Nigeria

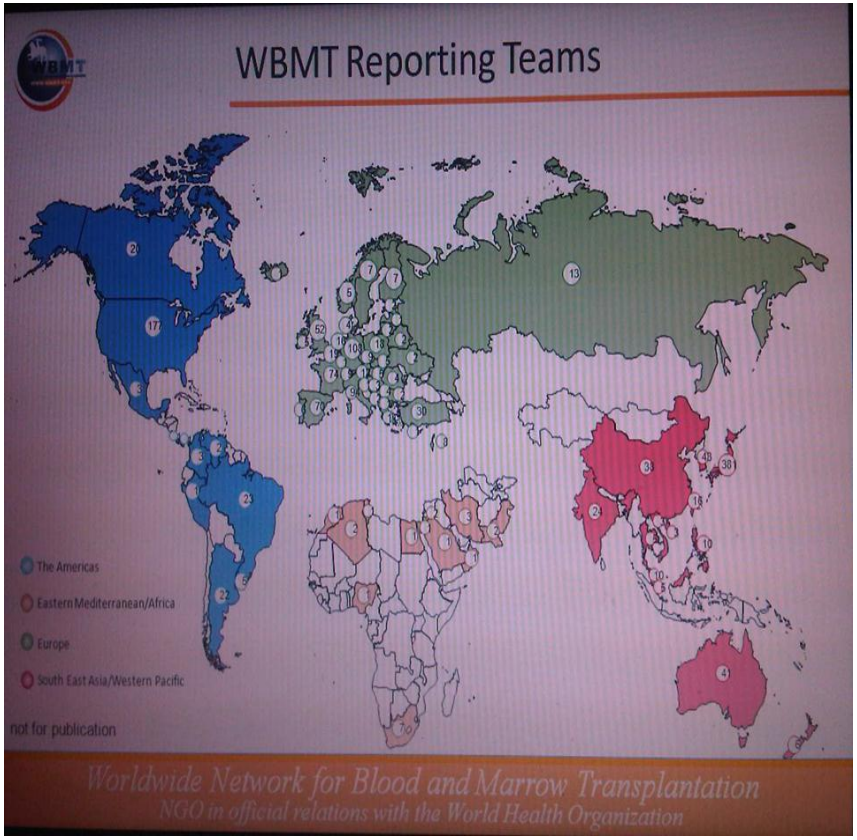
INTRODUCTION

- VOD usually occurs within 3 weeks of HSCT
- Prevalence is 0-60% depending on the risk factors
- Mortality up to 80% by day 100 in established severe cases
- It can also occur in solid organ transplant
- No uniform consensus on the optimal strategy for managing VOD

Centres performing HSCT in Nigeria

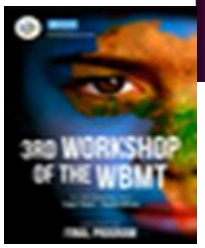
Nigeria performed first HSCT in 2011, only centre in West, Central and East Africa

36 states,170 million, only one centre of HSCT at UBTH in Benin city Edo State Nigeria



NGBMT 2013 REPORT

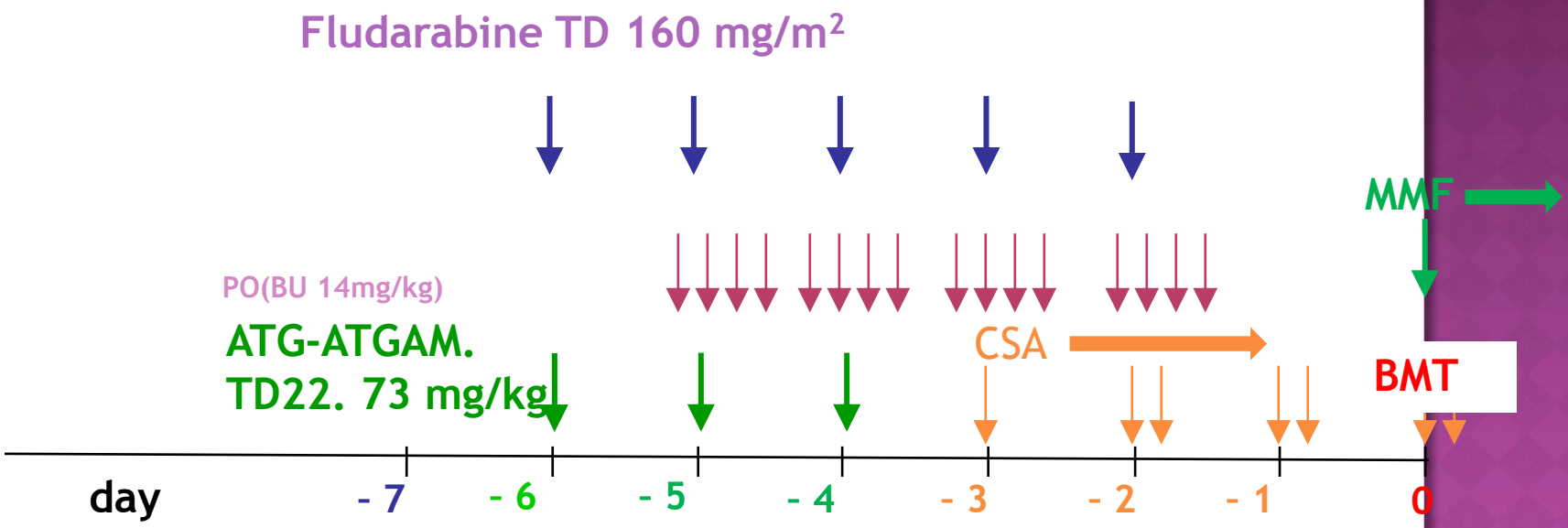
PATIENTS	AGE/SEX	DONOR AGE/SEX	DATE OF HSCT/DOSE	CONDTN/ GVHD PREVENTION	ABO/CMV (R/D)	ENGRAFTMENT(NEU/PLT)	CHIMERISM/ GVHD/SATUS
NM	7yrs/M	MSD(14/M)	Sept 2011 /9.2X10^8/kg	FLU/BU(ATG, CSA,MMF)	O+,CMVNeg/ 0+,CMV Neg	+18/+21	95%(2yrs)No GVHD,Alive
AM(1st HSCT)	12yrs/M	MSD(19/F)	Aug 2012 /5.7X10^8/kg	FLU/BU(ATG, CSA,MMF)	A+,CMV+/O+ ,CMV+	Rejection (Self at +42)	0%,No GVHD,Alive
AM(2nd HSCT)	13yrs/M	MSD(20/F)	May 2013 9.2X10^8/kg	BU16mg/kg/ CY100mg/kg(cy100mg/kg+ 3,+4)	A+,CMV+/O+ ,CMV+	Rejection (High persistent fetal hemoglobin)	0%,NO GVHD,Alive
ME	15yrs/M	MSD(21/F)	July2013 8.2X10^8/kg	FLU/BU(ATG, CSA,MMF)	O+,CMV+/O+ CMV+	+18/+22	96%(8mths), no GVHD,Alive



UBTH Protocol:

BU/Flu-RIC regimen

For SCD and matched sibling donor



Features and Risk factors of HSCT patients in Nigeria

INCIDENCE OF VOD IN NIGERIA IS 0% (NGBMT 2013 REPORT)

Risk factors for VOD

- Pre-Transplant iron over load (Carreras et al 1988)
- Stem cell source was Allogeneic (Allo>Auto)
- Second patient had a second HSCT (McDonald et al 1993)
- All had Busulphan with Fludarabine but second patient had added cyclophosphamide (Casaro et al 2005).
- All were paediatric patients with 33.3% as 7yrs (Casaro et al 2005)

Other factors for consideration

- No pre-existing liver disease
- All had RIC conditioning (Hogan et al 2004)

Assessment/Prevention of VOD in patients with risk factors

- Full liver enzyme assessment before HSCT especially Bilirubin and every other day
- Reducing iron over load with chelators
- Daily weighing and measurement of liver span of patients
- Weekly USS to assess liver
- Daily fluid balance
- Use of RIC regimen
- Combine fludarabine with Busulphan
- Use of Unfractionated Heparin(100mg/kg continuous daily)for central line
- Occasional use of methylprednisolone

Key challenges and the future

* Diagnosis of VOD

- Trained personnel
- MRI (Gadotexic acid enhanced MRI more specific for VOD)
- Hepatic Histology

*Drugs

- Defibrotide

* Data

Conclusions

- Data from Nigeria still small to make any significant conclusions
- Need for improved prophylaxis
- Need for training of personnel to improve diagnosis skills for VOD

Discussion

Chairmen

Thank you for attending

Please complete your feedback forms

Satellite Symposium sponsored by an
unrestricted grant from Jazz Pharmaceuticals