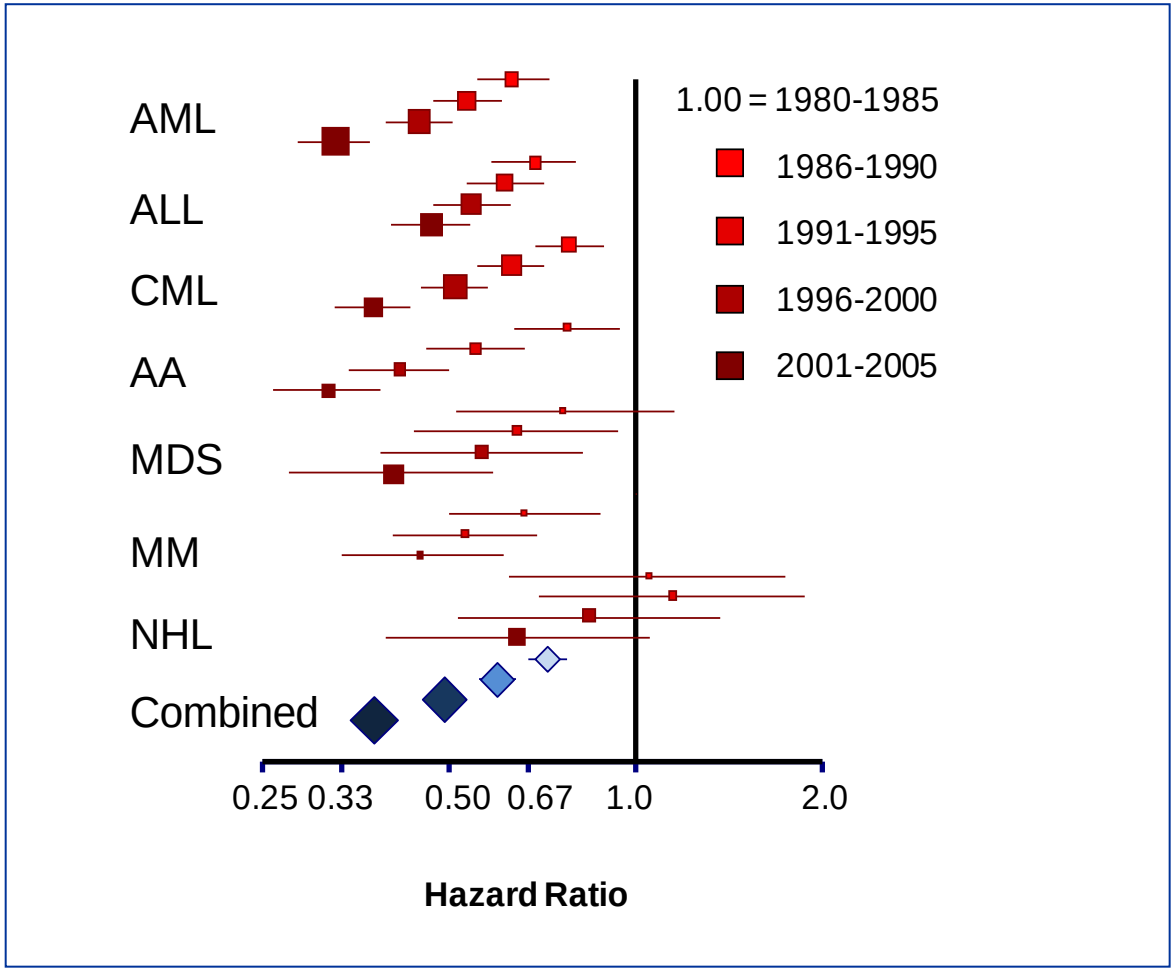
Complications after HSCT

D. Niederwieser
University of Leipzig
Germany

Complications after HSCT

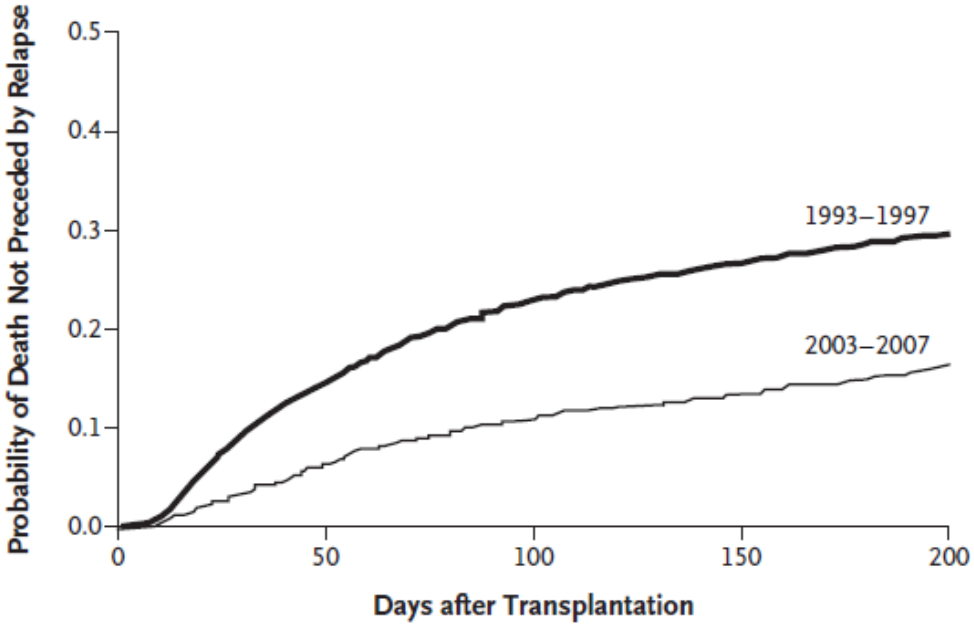
Transplant Related Mortality Decrease over time



Gratwohl et al, Cancer, 2009

Complications after HSCT

Probability of Death Not Proceeded by Relapse



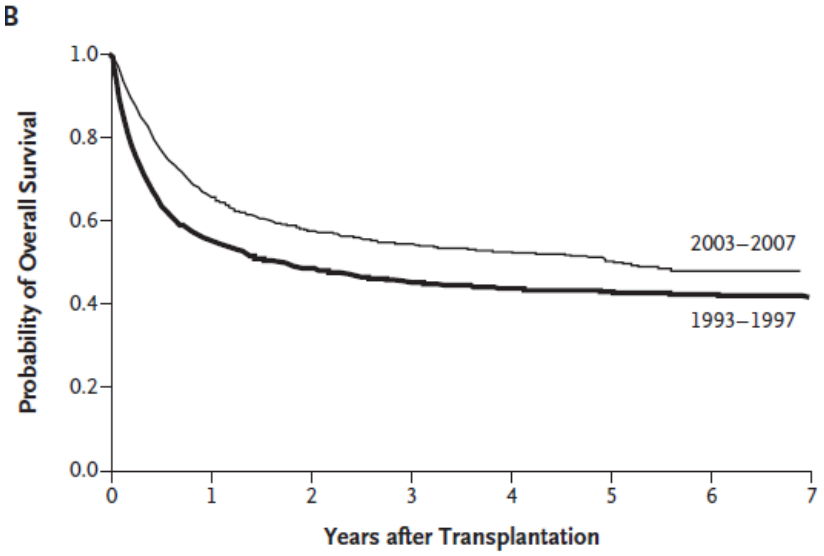


Figure 1. Probability of Death by Day 200 Not Preceded by Relapse and of Overall Survival during Two Time Periods.

Panel A shows the probability of death not preceded by relapse, and Panel B shows the probability of overall survival. Data on patients who were alive after 7 years were censored at 7 years for graphic purposes only.

Gooley et al, NEJM 2010

Complications after HSCT

Transplant Related Mortality Decrease over time

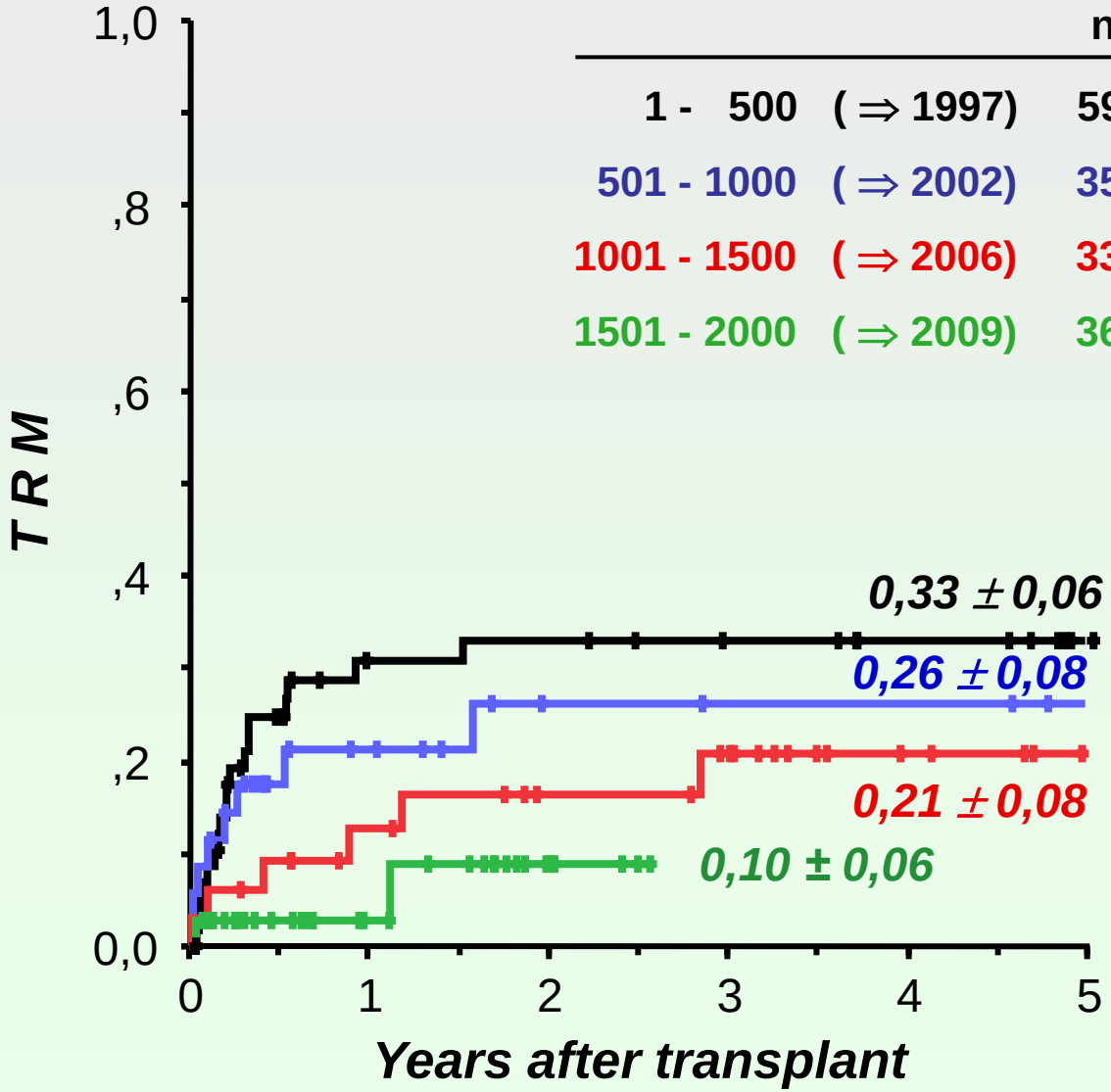
Table 2. Comparison of Outcomes, Organ Dysfunction, Infection, and Acute GVHD after Transplantation between the Two Time Periods.*

Variable	1993–1997 (N=1418)	2003–2007 (N=1148)	All Patients		Patients Who Underwent Myeloablative Conditioning	
			Adjusted Hazard or Odds Ratio (95% CI)†	P Value	Adjusted Hazard or Odds Ratio (95% CI)†	P Value
	no. (%)					
Outcomes						
Death not preceded by relapse						
At day 200	419 (30)	186 (16)	0.40 (0.32–0.49)	<0.001	0.44 (0.36–0.54)	<0.001
Overall	580 (41)	297 (26)	0.48 (0.40–0.57)	<0.001	0.48 (0.40–0.58)	<0.001
Relapse or progression of a malignant condition	379 (27)	302 (26)	0.79 (0.66–0.94)	0.008	0.82 (0.68–0.99)	0.04
Death from any cause	891 (63)	545 (47)	0.59 (0.52–0.67)	<0.001	0.61 (0.53–0.69)	<0.001
Liver dysfunction through day 100						
Elevated peak total serum bilirubin‡						
≥4 mg/dl	677 (48)	232 (20)	0.26 (0.21–0.32)	<0.001	0.28 (0.23–0.35)	<0.001
≥10 mg/dl	287 (20)	64 (6)	0.22 (0.16–0.30)	<0.001	0.24 (0.17–0.33)	<0.001
Hepatic GVHD§						
Stage 3 or 4	165 (12)	25 (2)	0.15 (0.09–0.24)	<0.001	0.18 (0.11–0.29)	<0.001
Stage 4	78 (6)	2 (<1)	0.03 (0.01–0.12)	<0.001	0.04 (0.01–0.17)	<0.001
Acute kidney injury through day 100						
Elevated creatinine						
Twice the baseline level	710 (50)	384 (33)	0.47 (0.39–0.56)	<0.001	0.46 (0.38–0.56)	<0.001
Three times the baseline level	257 (18)	115 (10)	0.48 (0.37–0.64)	<0.001	0.51 (0.38–0.68)	<0.001
Condition requiring dialysis	112 (8)	58 (5)	0.62 (0.42–0.90)	0.01	0.72 (0.49–1.07)	0.10
Pulmonary complications through day 100						
Condition requiring bronchoscopic evaluation	272 (19)	242 (21)	0.91 (0.75–1.12)	0.38	0.90 (0.73–1.12)	0.34
Respiratory failure	211 (15)	131 (11)	0.64 (0.49–0.82)	0.001	0.69 (0.53–0.90)	0.007
Infections through day 100						
CMV infection among CMV-seropositive patients¶	420 (57)	419 (63)	1.02 (0.87–1.20)	0.77	1.04 (0.88–1.23)	0.63
CMV disease among CMV-seropositive patients¶	62 (8)	33 (5)	0.52 (0.32–0.85)	0.009	0.53 (0.31–0.89)	0.02
Gram-negative bacteremia	213 (15)	129 (11)	0.61 (0.48–0.79)	<0.001	0.57 (0.44–0.75)	<0.001
Invasive mold infection	125 (9)	80 (7)	0.49 (0.35–0.71)	<0.001	0.55 (0.38–0.78)	<0.001
Invasive candida infection	99 (7)	10 (1)	0.12 (0.06–0.25)	<0.001	0.15 (0.08–0.29)	<0.001

Gooley et al, NEJM 2010

Transplant related mortality after conventional allogeneic SCT: AML in CR1 / CR2 / PR1 (1stTx)

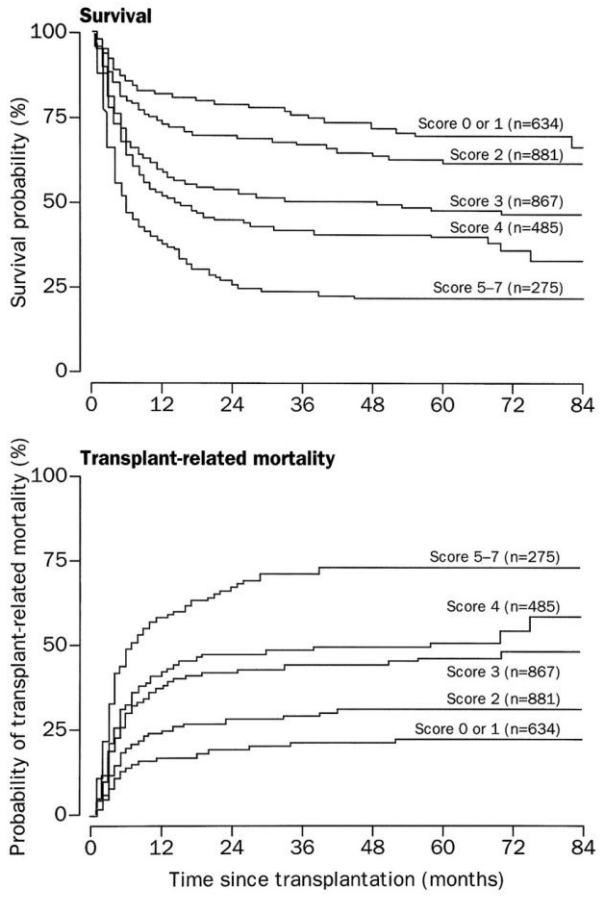
	n	age	RD / URD
1 - 500 (⇒ 1997)	59	*32* (17-55)	57 / 2
501 - 1000 (⇒ 2002)	35	*38* (17-53)	24 / 11
1001 - 1500 (⇒ 2006)	33	*37* (13-54)	16 / 17
1501 - 2000 (⇒ 2009)	36	*42* (19-55)	17 / 19



Hematology/Oncology
Univ. Hospital
Leipzig

The role of SCT on the path to cure

Main risk factors



- Age
  - < 20y; 20-40 y; > 40y
- Stage
  - cP; aP; bc
- Time interval
  - < 12 mo; > 12 mo
- Donor
  - sex
    - dfrm; other
  - histocompatibility
    - HLA-id sib; other

Lancet, 1998

Risk score for SCT

Main risk factors

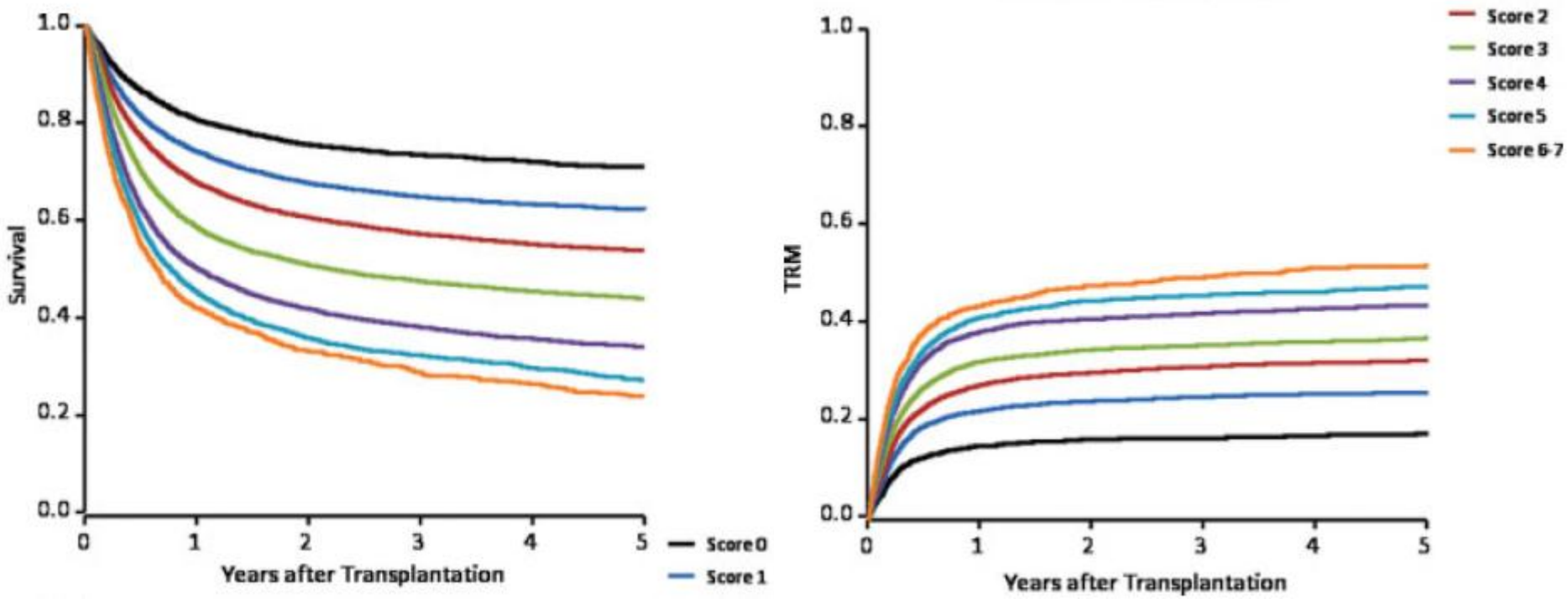


FIGURE 1. Survival (*Top*) and transplant-related mortality (TRM) (*Bottom*) of 56,605 patients with an allogeneic hematopoietic stem cell transplantation (HSCT) for an acquired hematological disorder is shown by risk score. Graphs reflect probability of survival (*Top*) and transplant-related mortality (*Bottom*) over the first 5 years after HSCT.

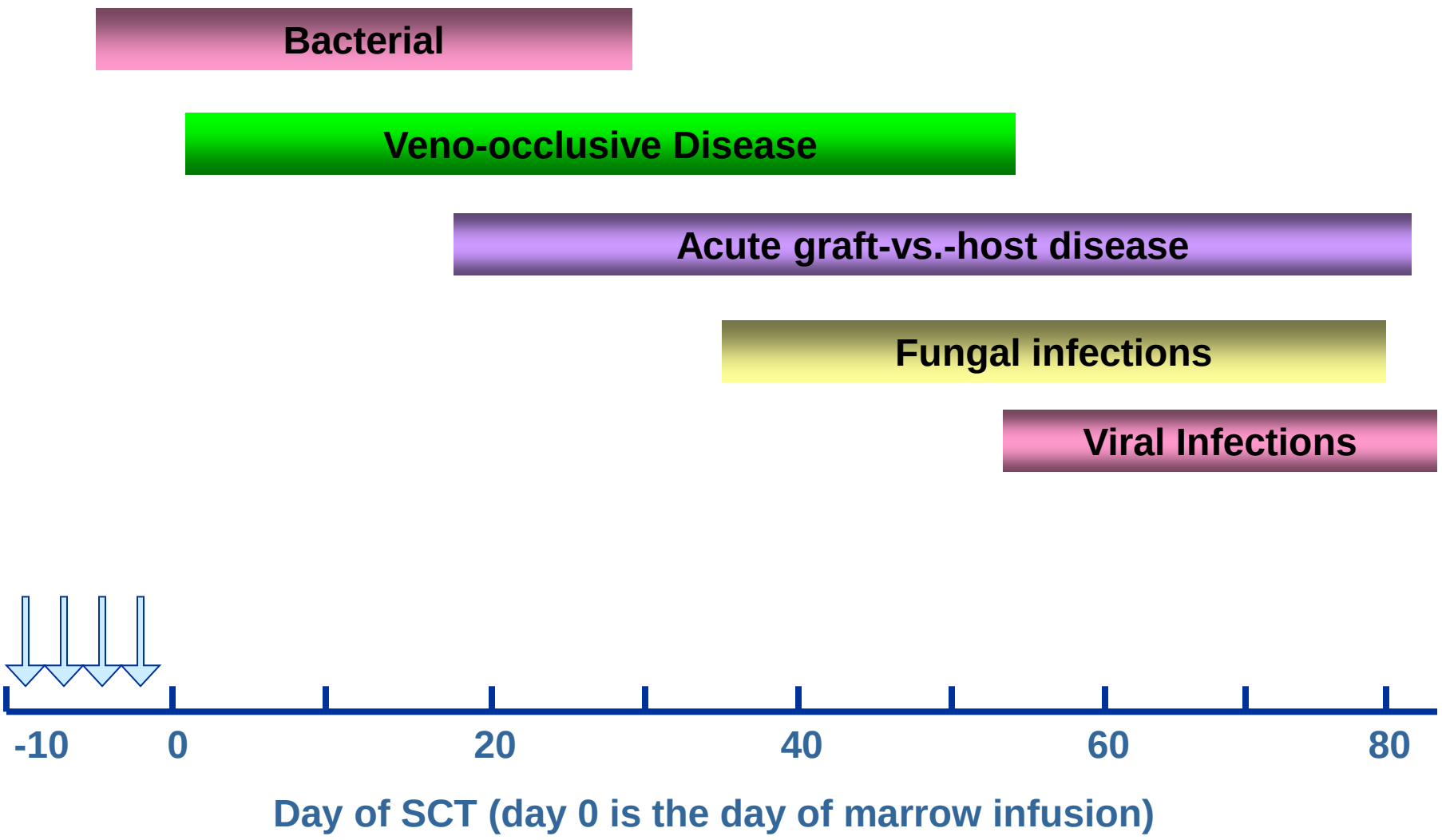
Gratwohl, Cancer 2009

Typical causes of Death after minimal conditioning

Seattle Konsortium

Died: 41%	
Causes of Death	Percent
Relapse / Progression	25
GVHD + Infections	11
Infections	2
Miscellaneous	3

Occurrence of complications after SCT



Complications after HSCT

Bacterial Infections

- Spectrum of bacterial infection has changed from gram - to gram + (intravascular catheters)
- Equivalent or higher numbers of bacteremias during post engraftment

- Streptococcus Pneumonia (Pneumonia/Meningitis)
- Antibiotic Resistant Bacteria (first line therapy, screening)
- Clostridium difficile colitis

Marr, KA Hematology 2012

Complications after HSCT

Late infections

Table 1. Late infections to consider for prevention strategies

Infection	Preventative strategies	Comments	Reference(s)
VZV, HSV	Prophylaxis, vaccination	Acyclovir and valacyclovir reduce morbidity in first year; safety of live-attenuated vaccine is not definitively demonstrated	13,17-19
CMV	Prophylaxis, preemptive monitoring	Ganciclovir-based prophylaxis and preemptive administration may reduce infection and associated death	20,21
Adenoviruses	Preemptive monitoring	Late infection may be more common than appreciated, but prevention strategies are lacking	23,24
Influenza	Vaccination and prophylaxis	Prophylaxis may be effective during outbreaks and vaccination can reduce morbidity, although not 100% effective	34-36
Respiratory bacterial pathogens	Prophylaxis, vaccination	Vaccination is critically important to reduce pneumococcal infection; prophylactic tm/slf may reduce some bacterial respiratory infections	7,8
TB	Pre-HCT screening with treatment	Latent infection should be diagnosed and treated to prevent reactivation late	8
Aspergillosis	Prophylaxis, preemptive monitoring	Randomized trials show efficacy of newer azoles such as posaconazole and voriconazole, although survival not measurably improved	35,36
P jiroveci pneumonia	Prophylaxis	trm/slf, administered daily or 2-3 times weekly is the most effective regimen; alternatives including dapsone and atovaquone available, but not definitively studied	40,41
Toxoplasmosis	Prophylaxis	trm/slf may reduce infection	46
Nocardia	Prophylaxis	trm/slf may reduce infection, although breakthrough occurs	46-48

Marr, KA Hematology 2012

Complications after HSCT

Late infections

Table 2. Viruses, seroprevalence, and annual attack rate estimated from the adult population

Latent viruses	Seroprevalence	Episodic viruses	Attack rate
CMV	45%-90%	RSV	5%-15%
EBV	> 90%	Parainfluenza	5%-10%
HSV1/2	50%-90%	Influenza	< 5%
HHV-6	> 90%	Adenovirus	< 5%
EBV	> 90%	Rhinovirus	< 5%
VZV	> 90%*	Meta-pneumovirus	?
BK virus	> 90%	Measles	< 1%

*Population estimates are changing based on vaccination decrease of natural infection.

Marr, KA Hematology 2012

Complications after HSCT

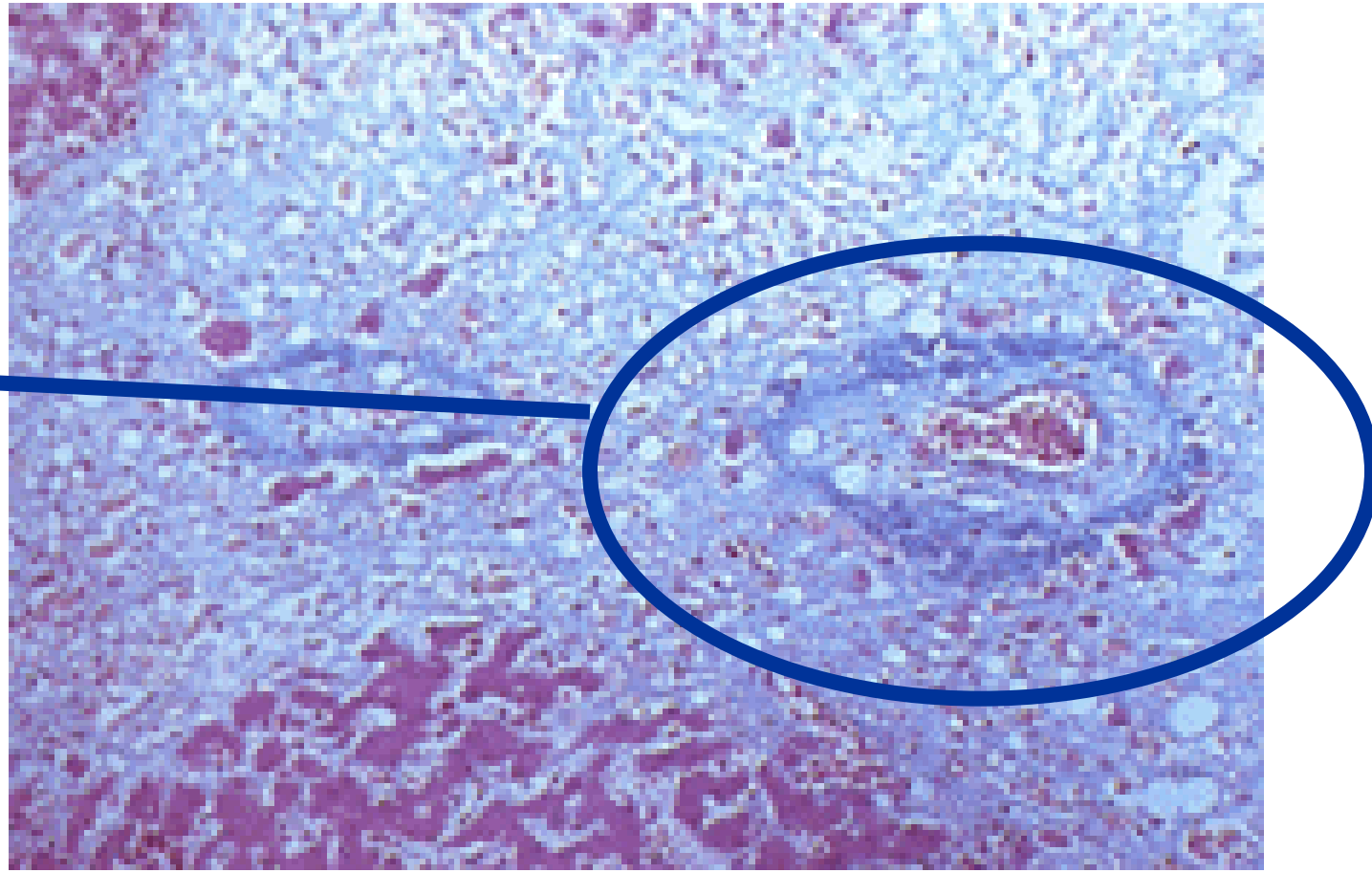
Non-infectious complications

- Graft-versus-Host disease
- Veno-occlusive disease
- Relapse

Complications after HSCT

Veno-occlusive disease

Occlusion of Hepatic Venules



After HSCT:

- occlusion of hepatic venules not seen at path ~ should syndrome be renamed?
- “Sinusoidal Obstruction Syndrome” [SOS] (vs VOD)

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

Deleve et al. Clin Sem Liver Dz. 2002

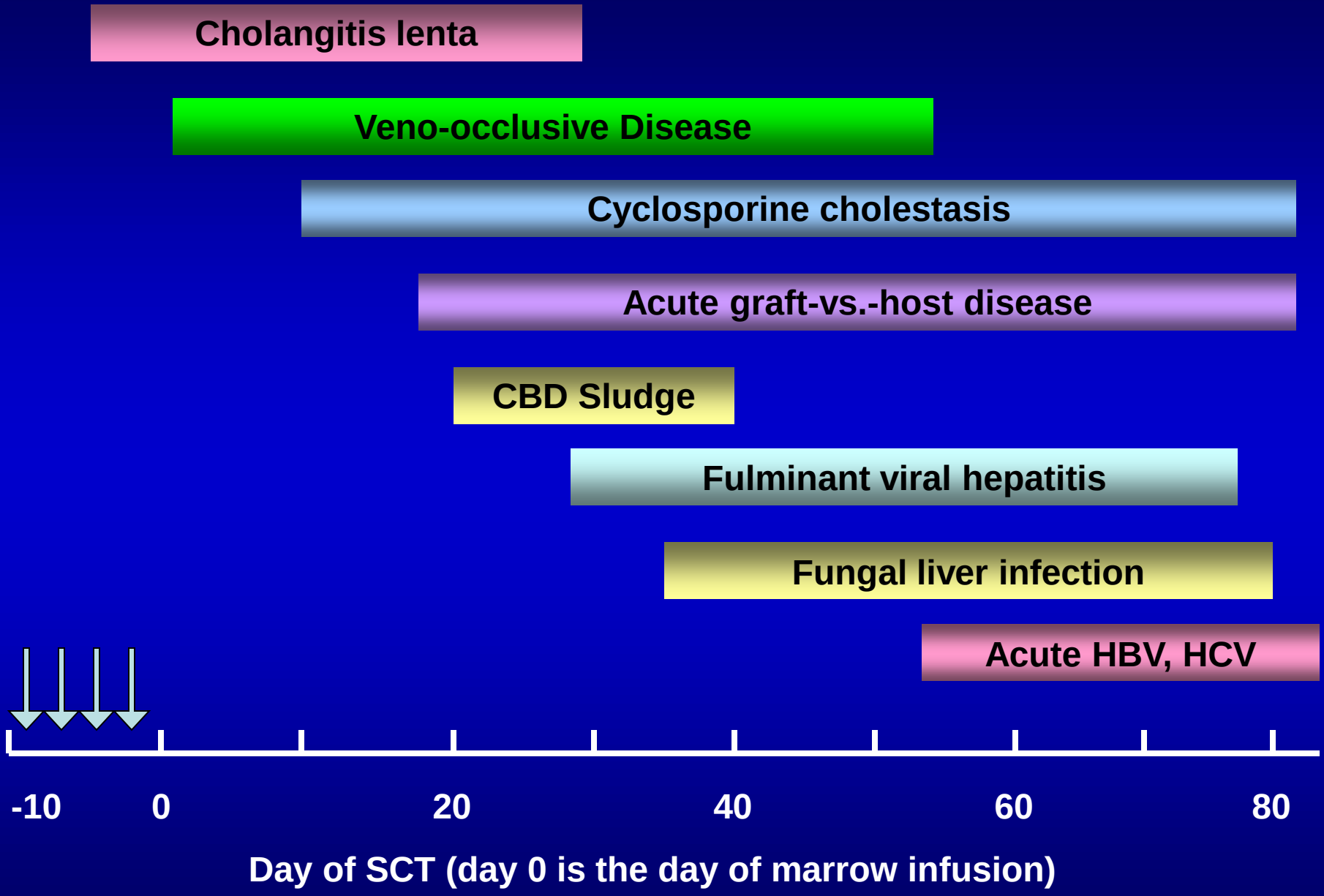
- Current Consensus: VOD (SOS)

Kumar et al, Mayo Clinic Proc. 2006

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 or, ▪ CNS dysfunction


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)

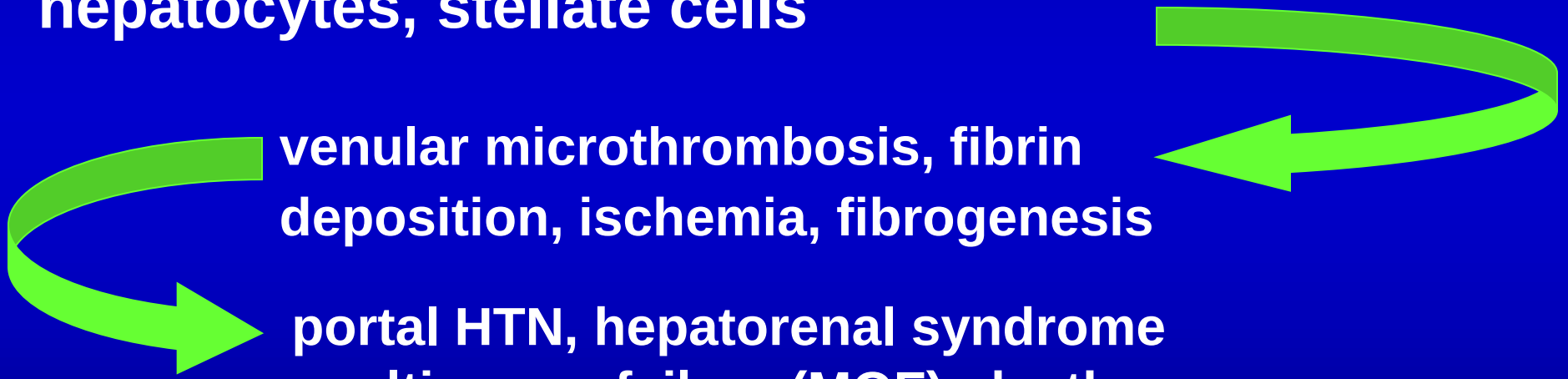
Ultrasound and CT in VOD

- 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

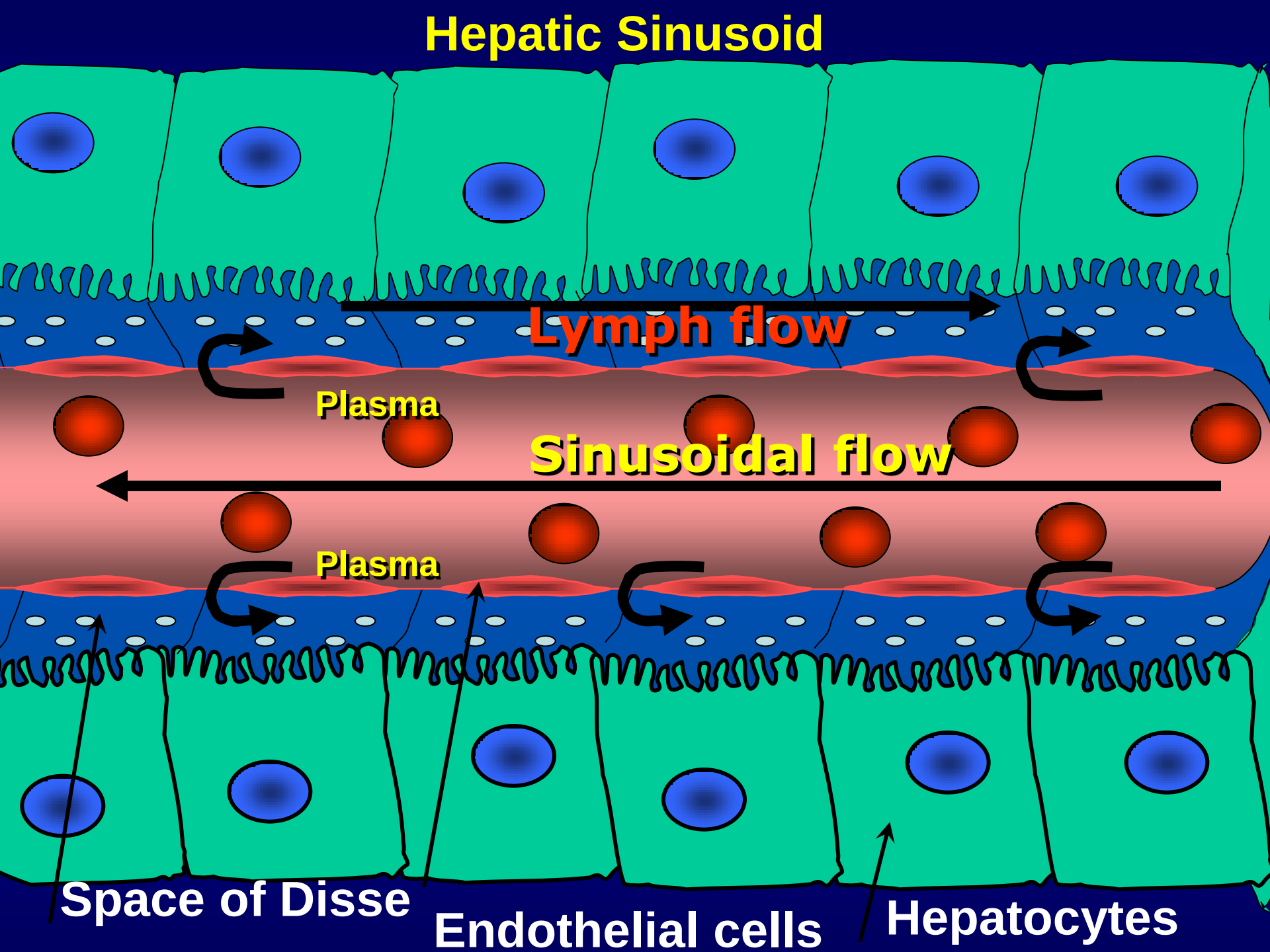
Hepatic VOD/SOS post SCT

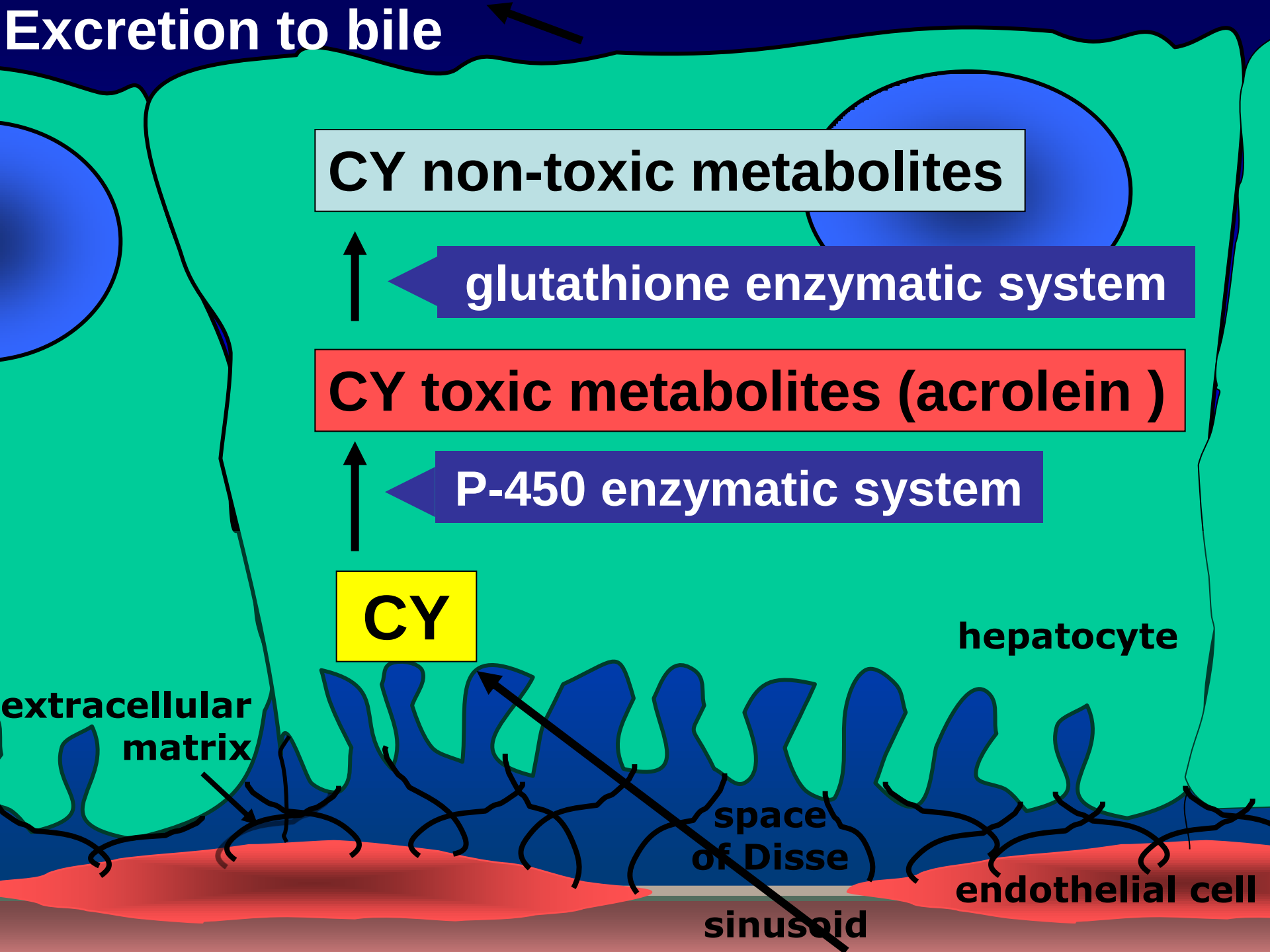
Pathophysiology:

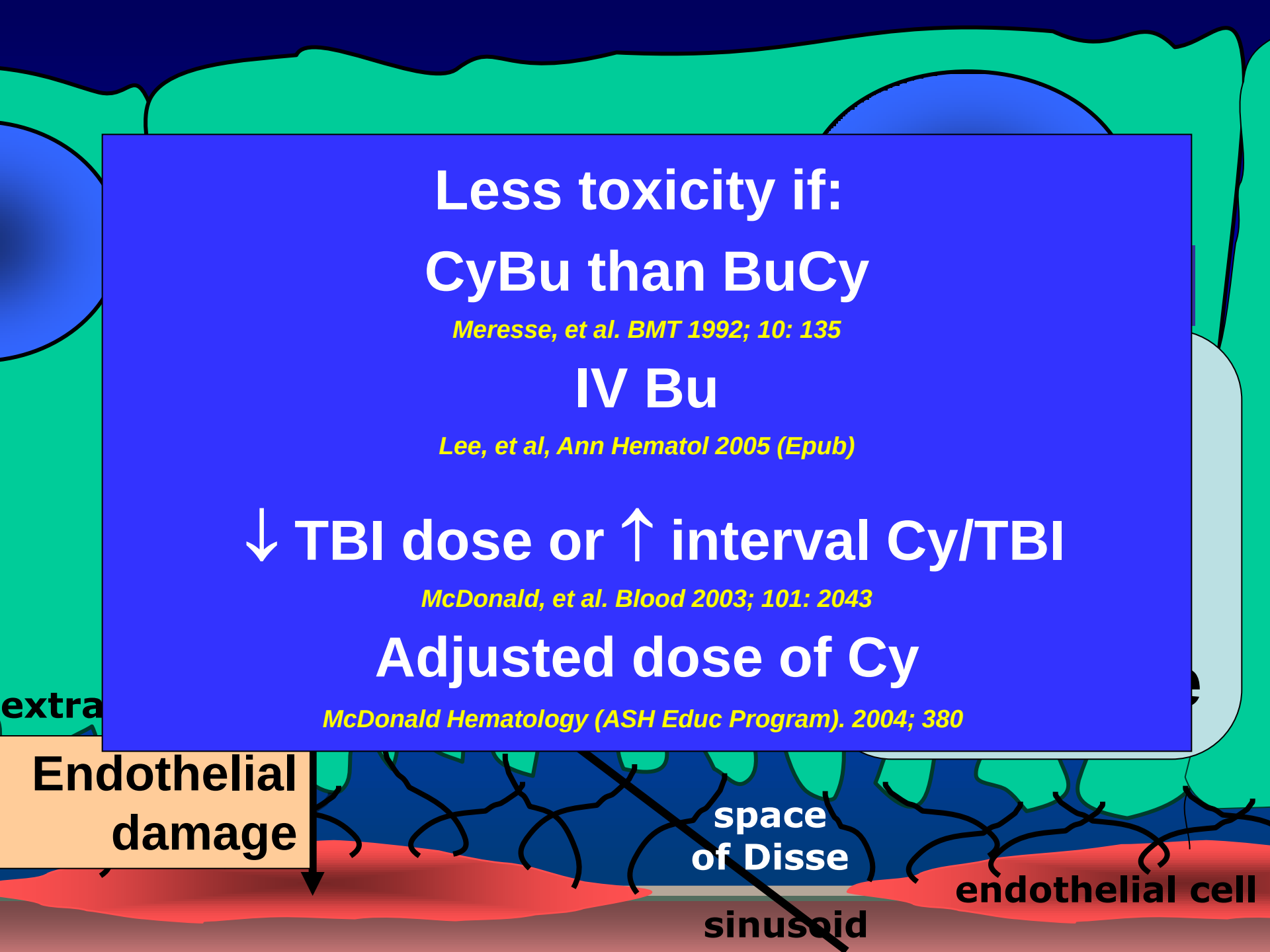
Primary injury to sinusoidal endothelial cells (SEC), hepatocytes, stellate cells

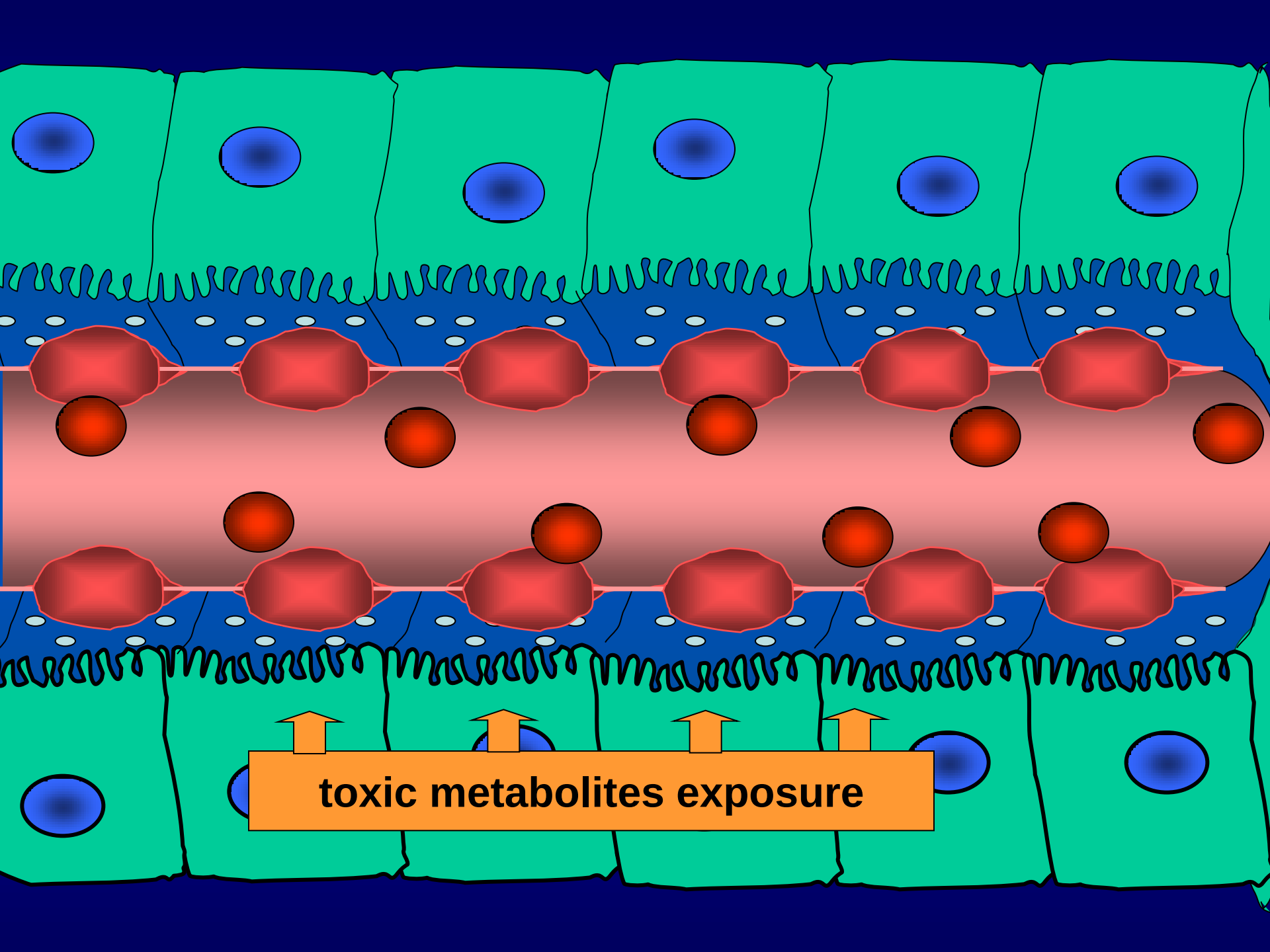


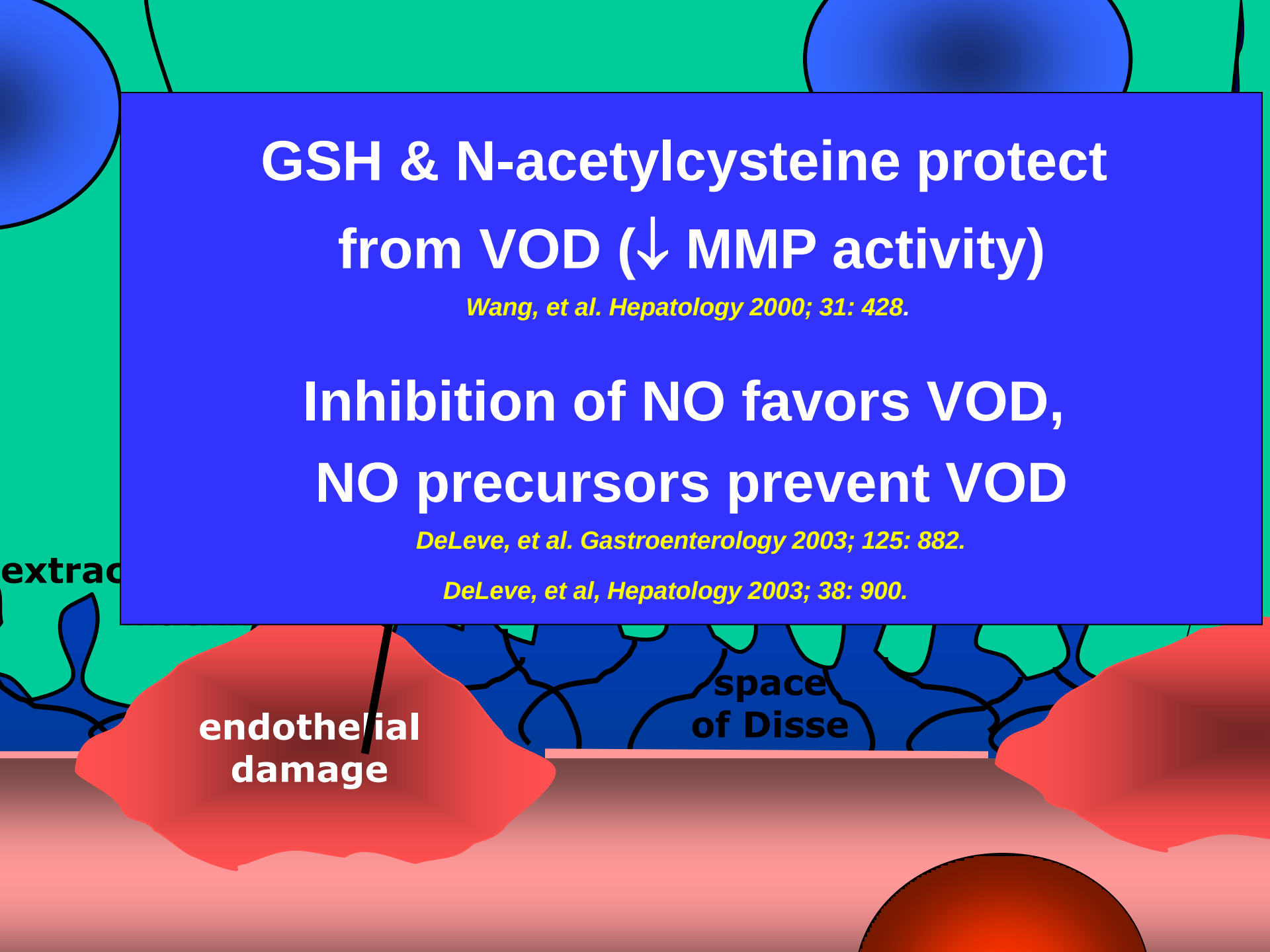
Richardson & Guinan BJH 1999; Ho et al , BMT 2008

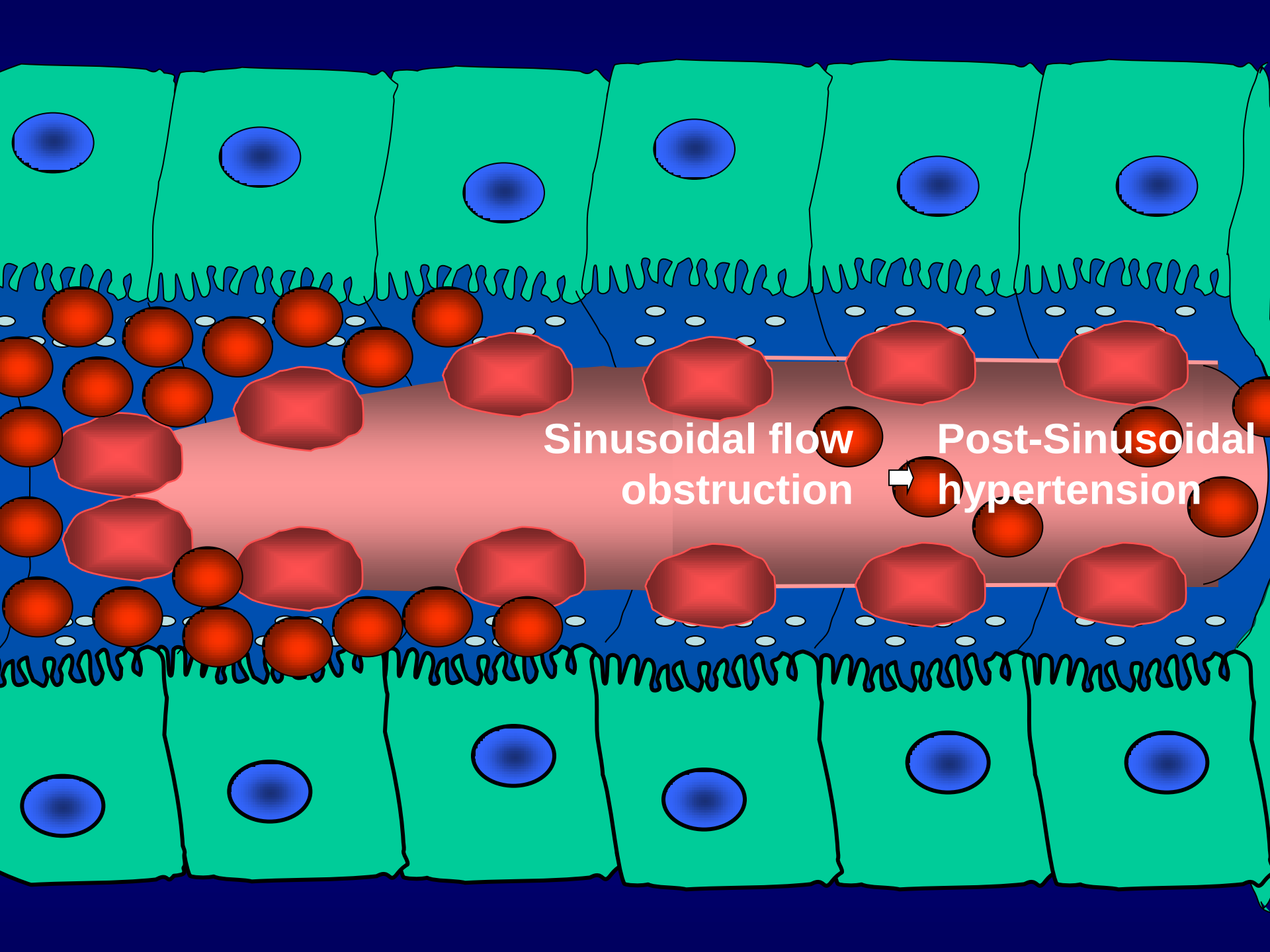

Hepatic Sinusoid
Lymph flow
Plasma
Sinusoidal flow
Plasma
Space of Disse
Endothelial cells
Hepatocytes

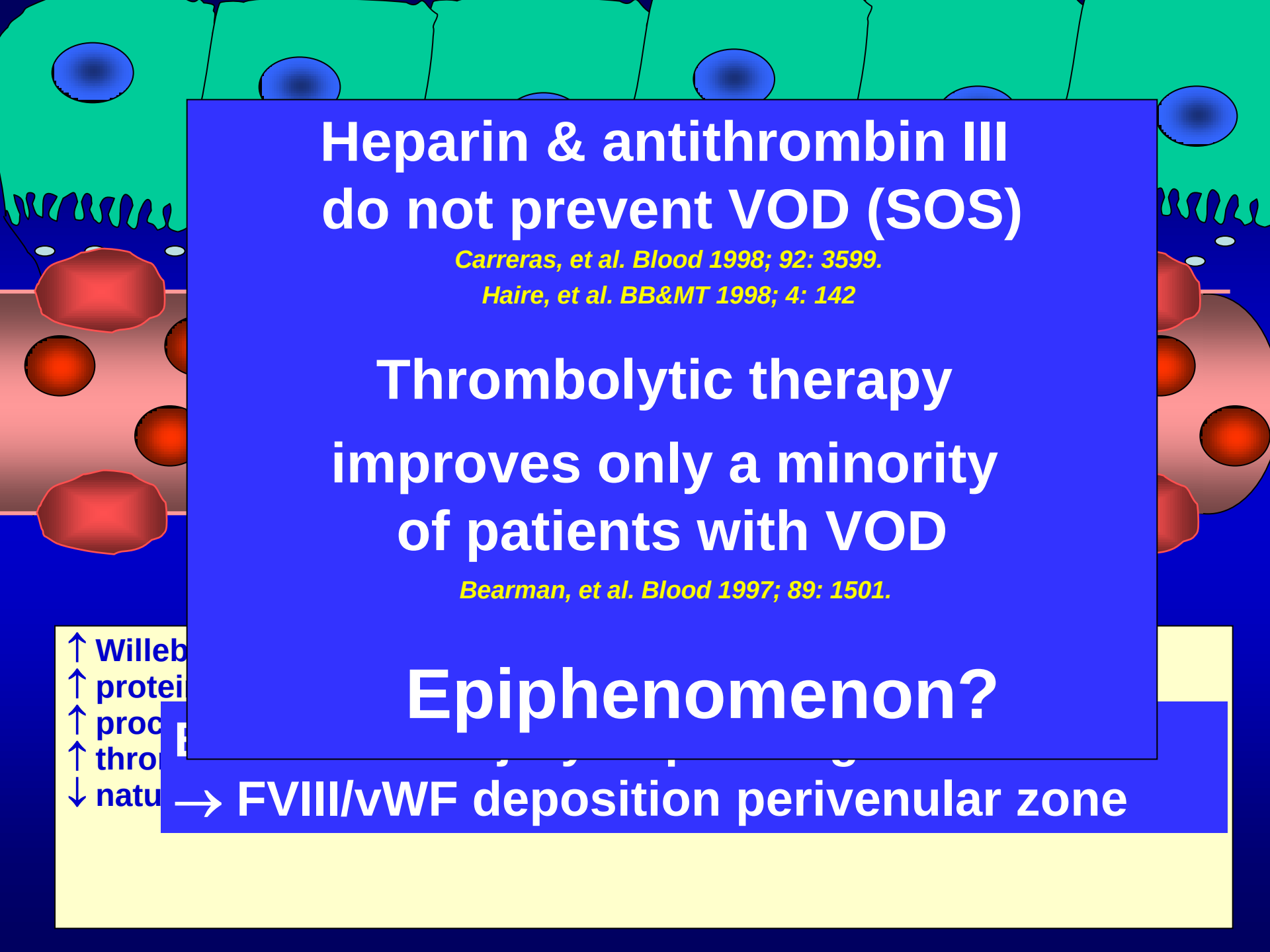

Excretion to bile
CY non-toxic metabolites
glutathione enzymatic system
CY toxic metabolites (acrolein)
P-450 enzymatic system
CY
hepatocyte
extracellular matrix
space of Disse
endothelial cell
sinusoid

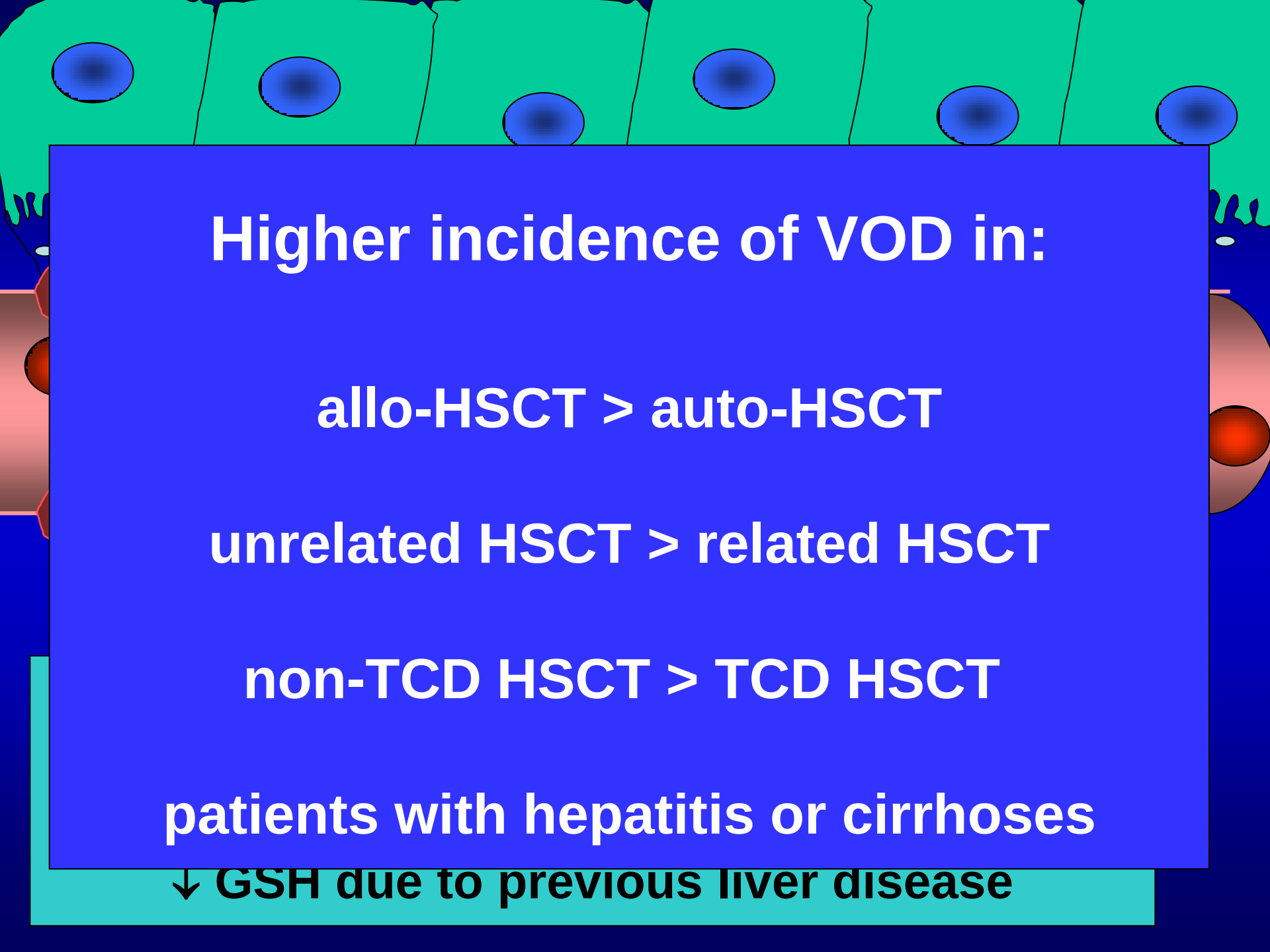

Less toxicity if:
CyBu than BuCy
Meresse, et al. BMT 1992; 10: 135
IV Bu
Lee, et al, Ann Hematol 2005 (Epub)
↓ TBI dose or ↑ interval Cy/TBI
McDonald, et al. Blood 2003; 101: 2043
Adjusted dose of Cy
McDonald Hematology (ASH Educ Program). 2004; 380
extra
Endothelial damage
space of Disse
endothelial cell
sinusoid


toxic metabolites exposure


GSH & N-acetylcysteine protect
from VOD (↓ MMP activity)
Wang, et al. Hepatology 2000; 31: 428.
Inhibition of NO favors VOD,
NO precursors prevent VOD
DeLeve, et al. Gastroenterology 2003; 125: 882.
DeLeve, et al, Hepatology 2003; 38: 900.
extrac
endothelial
damage
space
of Disse


Sinusoidal flow obstruction
Post-Sinusoidal hypertension


Heparin & antithrombin III
do not prevent VOD (SOS)
Carreras, et al. Blood 1998; 92: 3599.
Haire, et al. BB&MT 1998; 4: 142
Thrombolytic therapy
improves only a minority
of patients with VOD
Bearman, et al. Blood 1997; 89: 1501.
Epiphenomenon?
↑ Willeb
↑ protei
↑ proc
↑ thro
↓ natu
→ FVIII/vWF deposition perivenular zone



Higher incidence of VOD in:

allo-HSCT > auto-HSCT

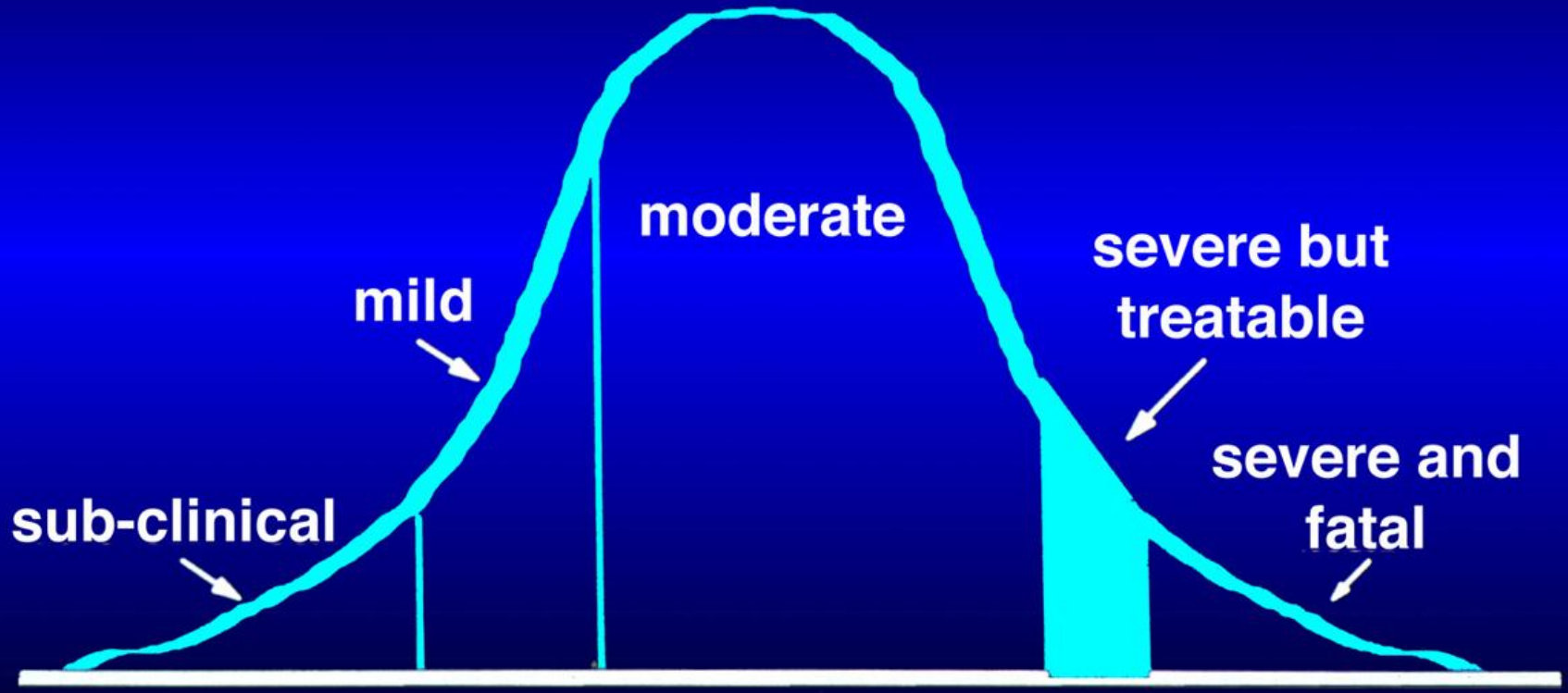
unrelated HSCT > related HSCT

non-TCD HSCT > TCD HSCT

patients with hepatitis or cirrhoses

↓ GSH due to previous liver disease

The clinical spectrum of VOD



Incidence of VOD over time Carreras et al

Table 2. Main Characteristics of the VOD Cases

	Seattle Criteria	Baltimore Criteria
VOD cases	117/845	73/845
Cumulative incidence of VOD	13.8% ± 1%	11.5% ± 1%
Diagnostic data; median (range)	Day +9 (0-44)	Day +8 (0-44)
Number of clinical criteria	(2:49*/3:68)	(3:57/4:16)
Clinical data: weight gain	115	73
Painful hepatomegaly	73	68
Ascites	21	21
Hyperbilirubinemia	114	73
MOF	26 (2.2)	26 (3.6)
Hemodynamic study	49	33
Mild-moderate VOD	79 (67.5)	38 (52)
Survived >+100 without VOD	56 (47.8)	31 (42.5)
Died <+100 without VOD	23 (19.7)	7 (27.4)
IP	9	1
Infection	5	2
GVHD	3	2
Graft failure	3	1
Relapse	2	1
Hemorrhage	1	—
Severe VOD [with MOF]	38 [26] (33)	35 [26] (48)
Died due to VOD	20 (19.7)	20 (27.4)
Died before +100 with VOD	7	5
Graft failure	3	3
Infection	3	1
GVHD	1	1
Died before +100 without VOD	3	3
IP	2	2
Infection	1	1
Alive >+100 without VOD	8 (6.8)	7 (9.6)
Mortality rate due to VOD (†)		
Whole series	17% ± 3%	27 ± 5%
<year 1997	17/72 (22% ± 5%)	17/44 (36% ± 7%)
≥year 1997	3/45 (9% ± 4%)	3/29 (14% ± 6%)
P value	0.06	0.04

MOF indicates multiorgan failure; IP, interstitial pneumonitis; GVHD, graft-versus-host disease, VOD, veno-occlusive disease.
In ( ) percentages.
*Only 5 of these patients fulfill the Baltimore criteria.
†Cumulative incidence.

Biol Blood Marrow Transplant 17: 1713-1720 (2011)

Incidence of VOD over time Carreras et al Risk Factors (multivariate analysis)

CML	(OR = 1.96; 95% CI=1.1-3.6)
MAC	(OR = 7.99; 95% CI=2.3-28)
MUD	(OR = 3.00; 95% CI=1.7-5.4)
previous liver disease	(OR = 3.40; 95% CI=1.7-6.6)
poor performance status	(OR = 3.20; 95% CI=1.8-5.7)

Death in patients with MOF:

treated with DF	2/8	(25%)	p=0.007
other treatment	14/18	(78%)	

Biol Blood Marrow Transplant 17: 1713-1720 (2011)

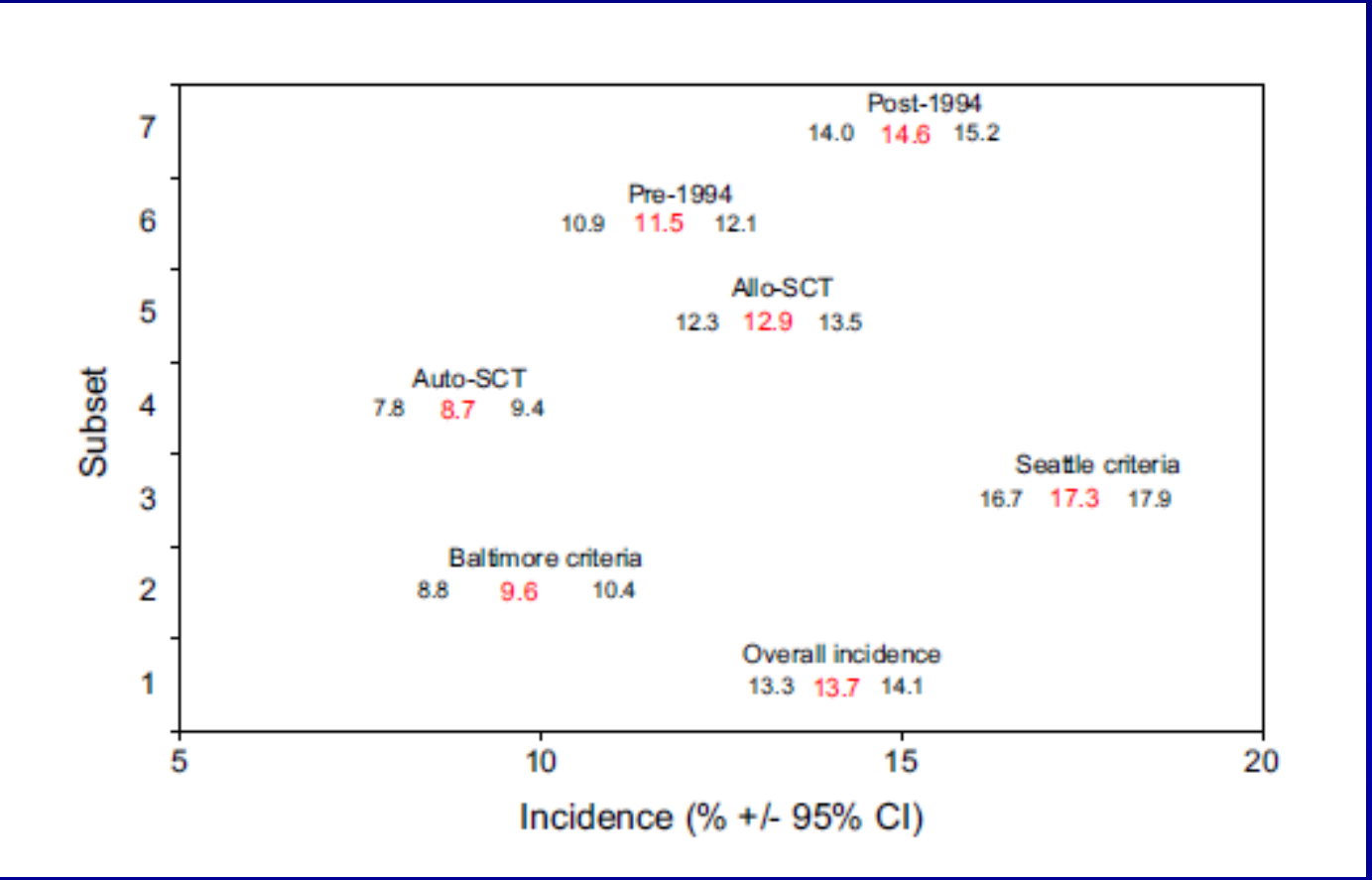
VOD incidence in 135 publications

Table 2. Descriptive Statistics for VOD Incidence from 135 Publications

Group	Number of Studies	Total Number of Patients	Number of Patients with VOD	Mean Incidence, %	95% CI	Min, %	Max, %	Median, %
1. All patients	135	24,920	3425	13.7%	13.3-14.1	0	62.3	13.3
2. Baltimore	33	5261	503	9.6%	8.8-10.4	0	28.9	8.6
3. Seattle	78	14,798	2565	17.3%	16.7-17.9	0	62.3	17.0
4. Auto-SCT	19	3967	344	8.7%*	7.8-9.4	1.5	44.1	6.2
5. Allo-SCT	67	11,285	1453	12.9%*	12.3-13.5	0	62.3	12.0
6. Pre-1994	50	10,943	1260	11.5†	10.9-12.1	1	62.3	9.3
7. Post-1994	74	12,234	1805	14.6†	14.0-15.2	0	53.3	15.4

*$P < .001$.
†$P < .05$.

VOD incidence in 135 publications



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

Rapamycin and VOD: DFCI retrospective review

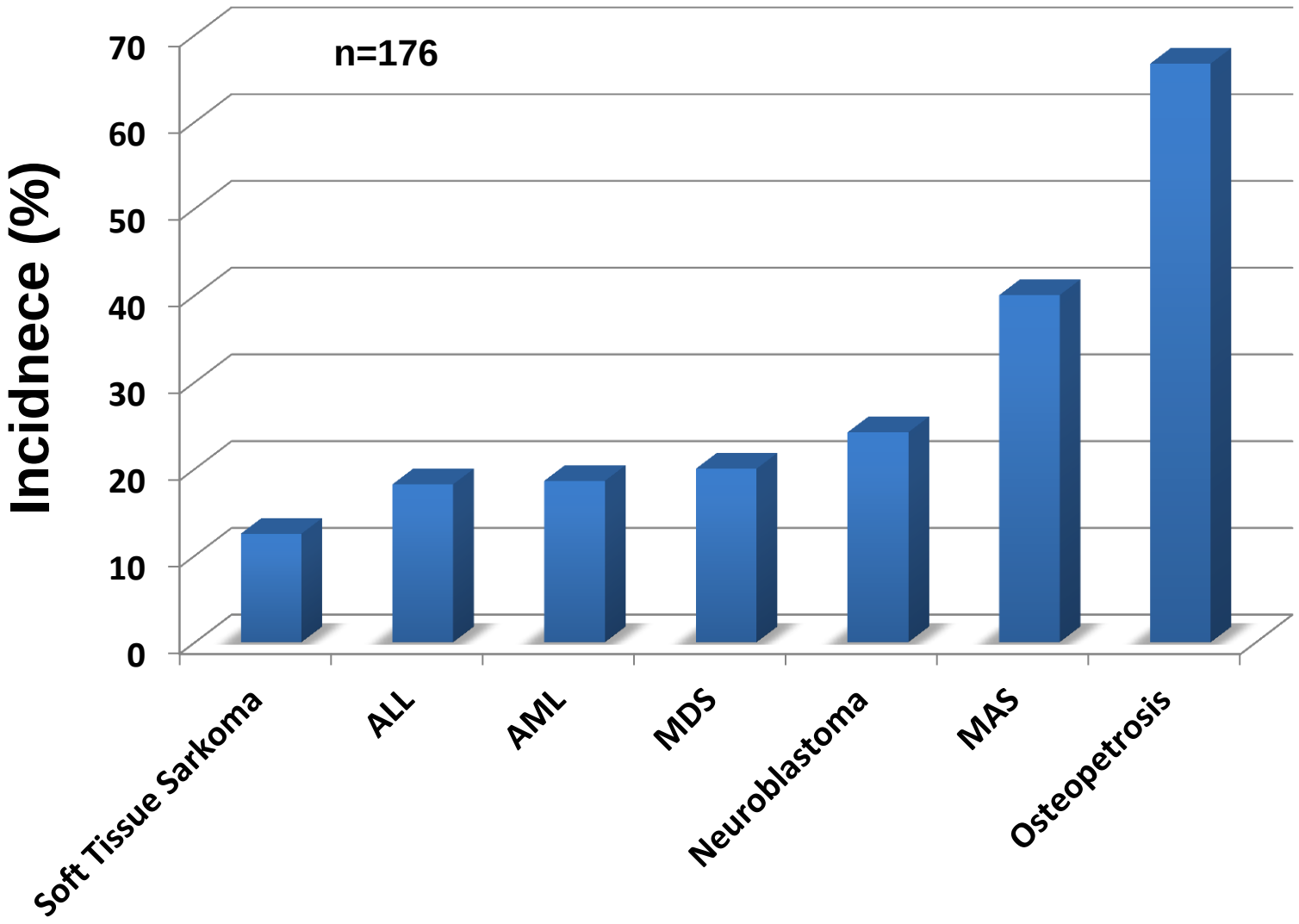
- All CyTBI-based transplants, 2000–2007
- Excluded:
  - Cord blood transplantation
  - Non-malignant disorders
- n=488, stratified by Sirolimus exposure
- Effect modulation by methotrexate co-administration
- Final groups:

	VOD Incidence	p value
– Tacrolimus – Methotrexate	16 (7%)	
– Tacrolimus – Methotrexate – Sirolimus	28 (21%)	p<0.001
– Tacrolimus – Sirolimus	15 (11%)	p=0.33

DFCI, Dana-Farber Cancer Institute;
CyTBI, cyclophosphamide and total-body irradiation

Cutler C et al. *Blood* 2008;112:4425–4431

Risk factors for VOD in Children



+Wolman‘s Disease (lysosomal acid lipase deficiency)

Mortality with VOD

Severe VOD = VOD with multi-organ failure

- **No approved treatment**
- **Current standard: best supportive care**

- Mortality in severe VOD: 84.3% J.A. Coppell et al. BBMT 2010

- Mortality in children with VOD:

  38.5% vs 9.5% in pts. without VOD (n=142 1993-2000) Barker et al, BMT ,2003

	Pts with VOD (n = 57)	Pts without VOD (n = 285)	P value *
Mortality by D+100, all causes	**24.6 %** (14)	**6 %** (17)	**< 0.0001**

* P-value from Chi-Square (Kaplan Meier Estimator)

The mortality in patients with VOD is 4 times higher than in patients without VOD

Overall Survival of patients with severe VOD

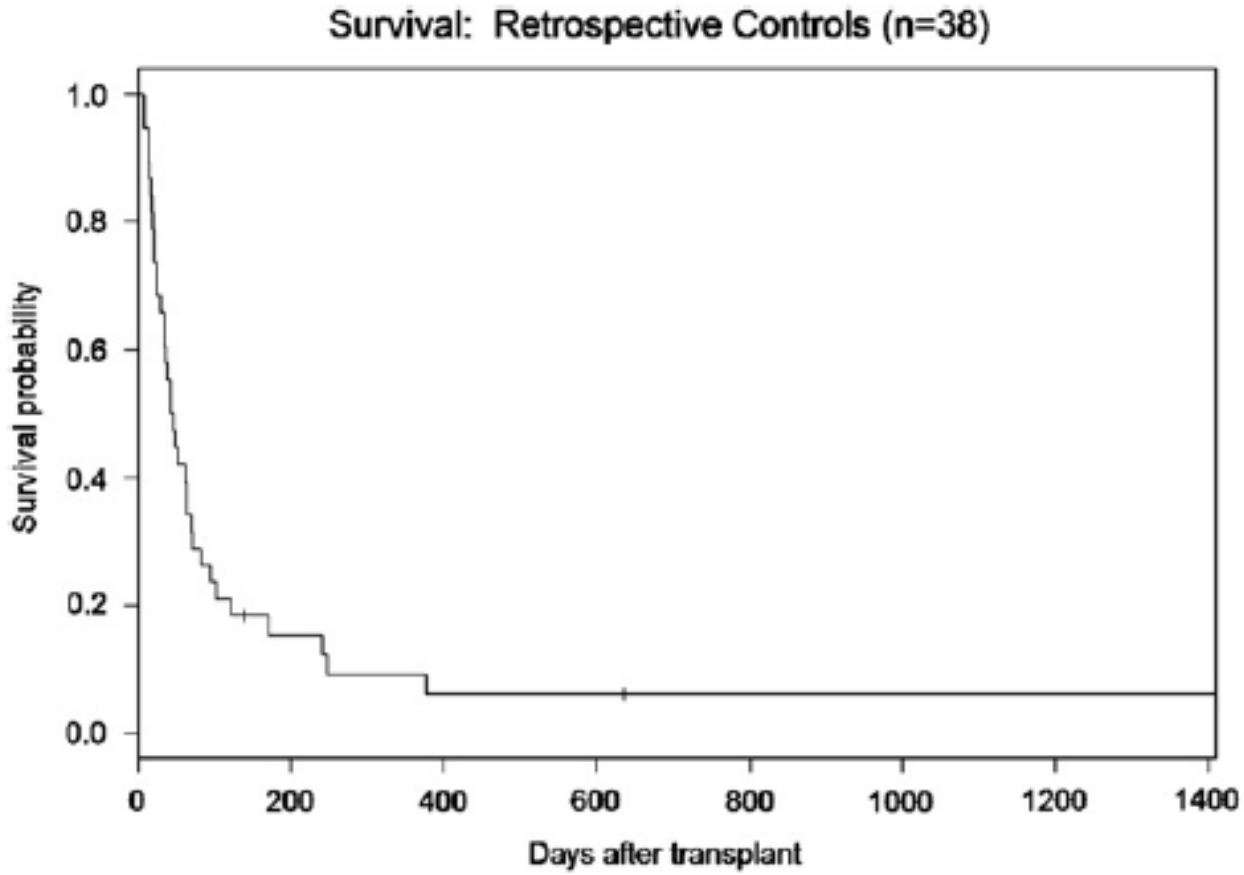
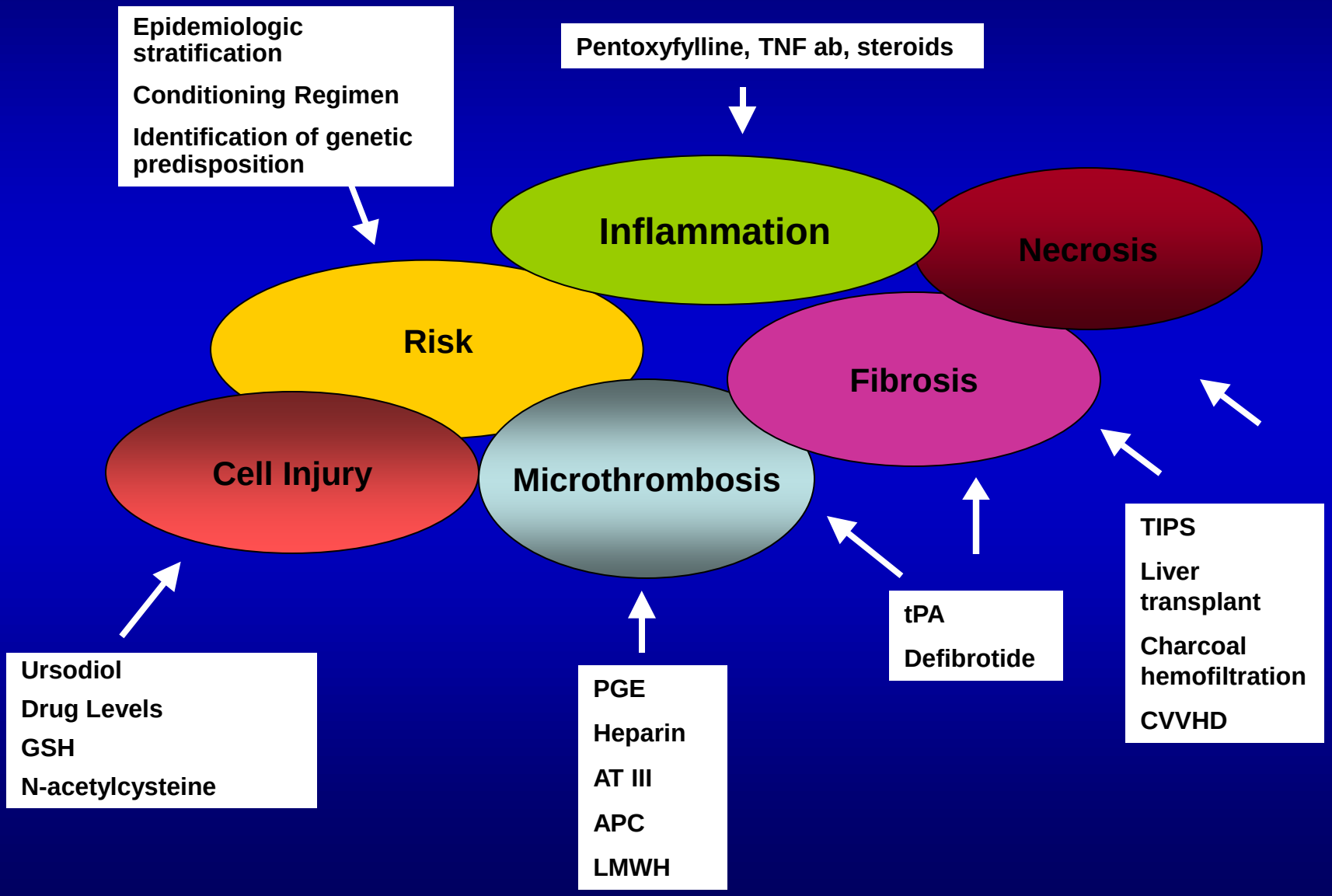


Figure 2. Kaplan-Meier survival curve for retrospective historical controls with severe VOD (MOF) (n = 38).

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

Potential Points for Intervention in VOD/SOS



Clinical experience with defibrotide in treatment of severe VOD with MOF

Author	Patients (n)	CR rate (%)	Day +100 Survival (%)
Richardson et al[1]	19	42	32
Chopra et al[2]	28	36	36
Richardson et al[3]	88	36	35
Corbacioglu et al[4]	22	50	36
Bulley et al[5]	14	60	79
Sucak et al[6]	6	50	50

CR, complete response

1. Richardson PG et al. *Blood* 1998;92:737–744;
2. Chopra R et al. *Br J Haematol* 2000;111:1122–1129;
3. Richardson PG et al. *Blood* 2002;100:4337–4343;
4. Corbacioglu S et al. *Bone Marrow Transplant* 2004;33:189–195;
5. Bulley SR et al. *Pediatr Blood Cancer* 2007;48:700–704;
6. Sucak GT et al. *Transplant Proc* 2007;39:1558–1563

Pivotal study of defibrotide for treatment of severe VOD (2005-01)

- **ITT population primary population for all efficacy:**
  - **All patients in the defibrotide group**
  - **32 patients for HC (selected by independent MRC)**

	DF patients (n=102)	HC (n=32)	Confidence Intervals*	P value**
CR (Day +100)	24% (24/102)	9% (3/32)	99% CI: -1–35% 95% CI: 3–30%	0.0148 (adjusted)** 0.0816 (unadjusted)
Mortality (Day +100)	62% (63/102)	75% (24/32)	95% CI: -32–3%	0.051 (adjusted)*** 0.0589 (unadjusted)

* For difference in CR rate

** p value for CR from Chi-Square test; p value for mortality from stratified Log-rank test

*** Adjusted by quintiles of propensity score based on four stratification variables; 1) allogeneic/autologous SCT, 2) adult/pediatric, 3) 1 or 2+ SCT, 4) ventilator/dialysis dependence

Strong correlation of CR to OS in both DF patients and HC ($p<0.0001$ and $p=0.0016$, respectively)

ITT, intent to treat;
MRC, Medical Review Committee; CI, confidence interval

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

Treatment IND trial (2006-05): effects of delayed treatment

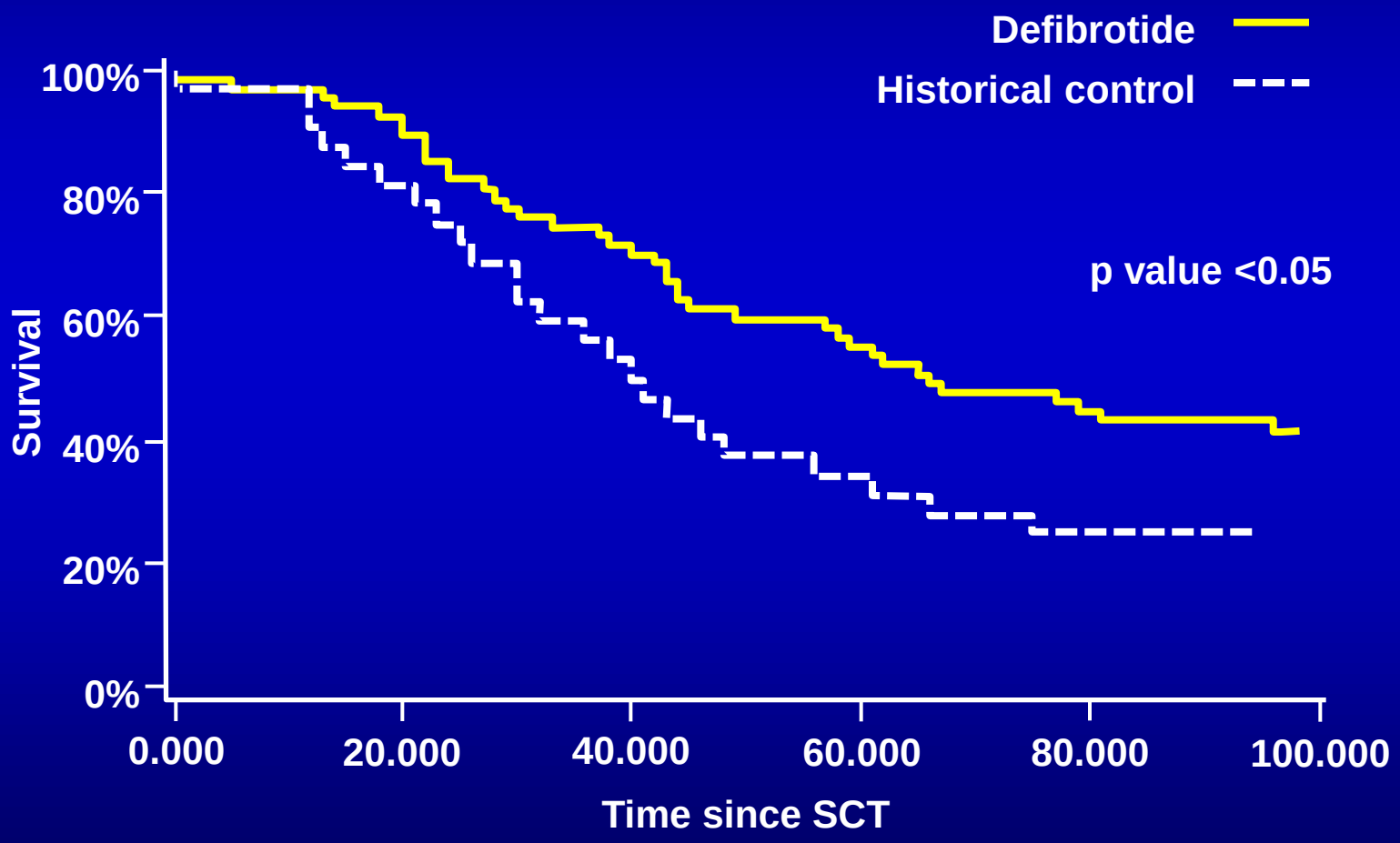
	Delay in treatment from diagnosis (n=103)*		
	≤2 days	>2 days	p value
Survival at Day +100	30/67 (45%)	8/36 (22%)	0.0237

* Data for one patient was missing at the time of analysis p values calculated based on the Chi-square test

Delay in the initiation of defibrotide treatment >2 days from diagnosis of VOD resulted in higher mortality at Day +100 post-SCT

Richardson P et al. *Blood (ASH Annual Meeting Abstracts)* 2010;116:906

Treatment IND trial (2006-05): defibrotide increases long-term survival



Richardson P et al. *Blood (ASH Annual Meeting Abstracts)* 2010;116:906

Results of pooled analysis

Results for CR and survival by Day +100:

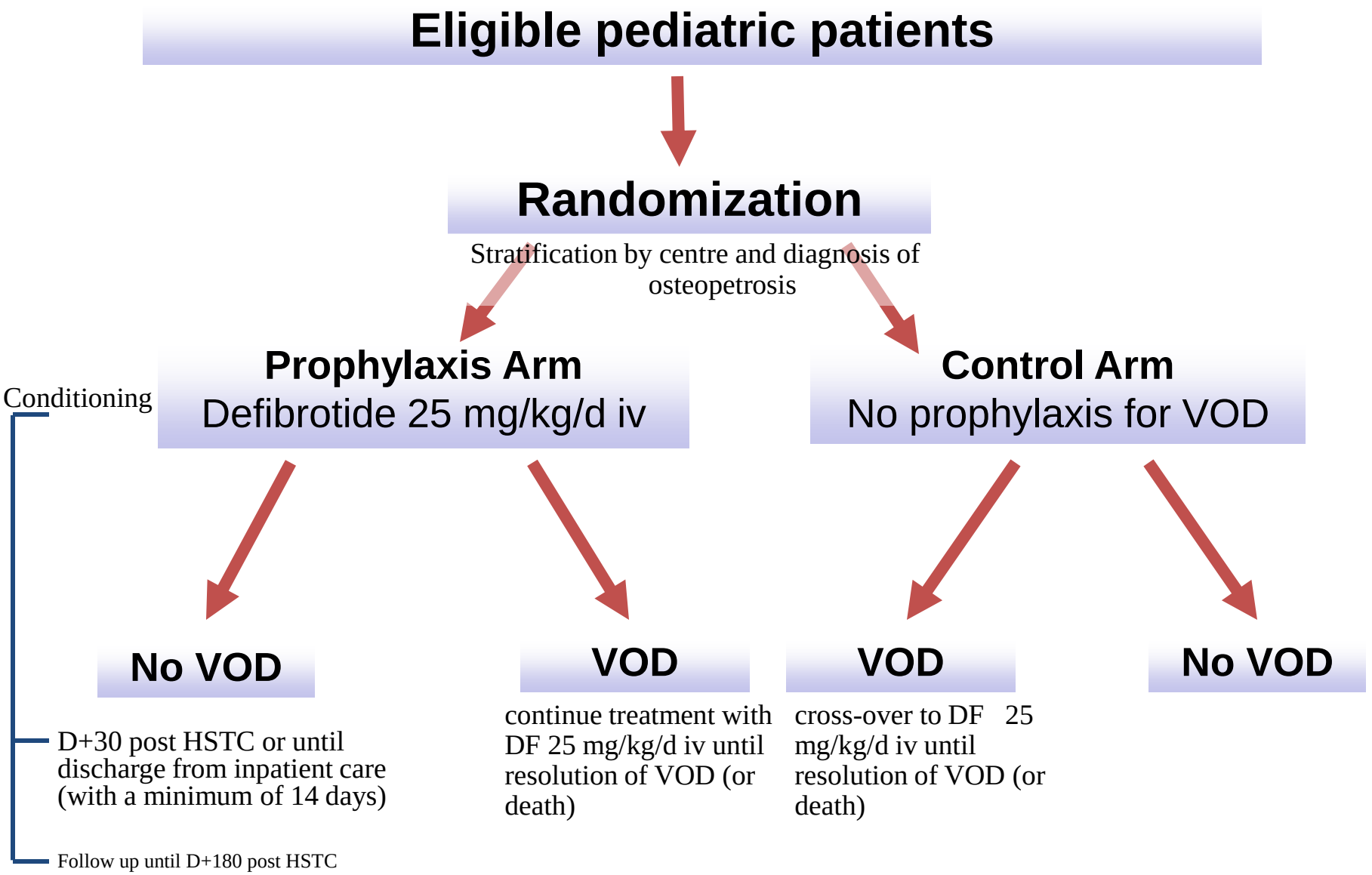
	DF Pooled (n=201)	HC (n=32)	Difference in rate (95% CI)	p value
CR (Day +100)	30% (61/201)	9% (3/32)	20.7 (7.9, 33.4) [1] 21.0 (2.3, 39.1) [2]	0.0015 [1] 0.0174 [2]
Survival (Day +100)	40% (81/201)	25% (8/32)	15.2%	0.0294 [3]

[1] Adjusted by quintiles of propensity score based on 4 stratification variables; 1) Allogeneic/autologous SCT, 2) Adult/pediatric, 3) Prior SCT, 4) Ventilator/dialysis dependence

[2] Exact Fisher test used for unadjusted analysis; p value for CR from Chi-Square test

[3] Unadjusted; p value for mortality from stratified Log-rank test

Study design



Primary Endpoint
Incidence of VOD by D+30

Intent-To-Treat Analysis

	DF Prophylaxis	Control	Hazard ratio (95% CI)	P value
Competing Risk:	12% (22/180)	20% (35/176)	-	**0.0488**
Kaplan Meier	12% (22/180)	20% (35/176)	1.69	**0.0507**

Per-Protocol Analysis

	DF Prophylaxis	Control	Hazard ratio (95% CI)	P value
Competing Risk:	11% (18/159)	20% (34/166)	-	**0.0225**
Kaplan Meier	11% (18/159)	20% (34/166)	1.91	**0.0234**

Baltimore Criteria	DF Prophylaxis	Control	p value **
Incidence of VOD at D+30	7% (13)	13% (23)	0.094

Secondary Endpoint Multi-Organ Failure

Consistent with the role of DF in endothelial protection, renal failure was significantly lower in the DF arm.

MOF (in all ITT pts)	DF (n = 180)	Control (n = 176)	Tot (n = 356)	P value*
Incidence of MOF	8% (14)	10% (18)	9% (32)	n.s.
• Respiratory Failure	8% (14)	9% (16)	8% (30)	n.s.
• **Renal Failure**	**1% (2)**	**6% (10)**	**3% (12)**	**0.017**
• Encephalopathy	1% (1)	2% (3)	1% (4)	n.s.

* P-value from Chi-Square Test

Analysis of secondary endpoint (score) of VOD associated MOF:

- Wilcoxon-Test for all patients: **p-value = 0.034**
- Wilcoxon-Test for patients with VOD at D+30: **p-value = 0.210**

Incidence and Severity of Graft versus Host Disease (GvHD)

Allogeneic SCT	DF Prophylaxis (n = 122)	Control (n = 117)	P value
Acute GvHD by D+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)	
Chronic GvHD by D+180	13% (16)	15% (17)	**0.751*****

* P-value from Chi-Square Test for incidence if GvHD by D+100
** P-value from Wilcoxon Test for Grading of GvHD by D+100
*** P-value from Chi-Square Test for incidence if GvHD by D+180

There were only two cases of Day+30 acute liver GVHD in the patients diagnosed with VOD, which suggests that there was minimal overlap between the two diagnoses.

Conclusion VOD / SOS

Cause:
- Regimen-related injury to the sinusoidal walls of the liver leading to obstruction of sinusoids and central veins

Incidence:
- 9-14%, Higher in children, estimated 3,500 case p.a. in EU
- Up to 60% in High Risk Groups

Outcome:
- A progressive disease ranging in severity from a mild to severe, associated with MOF (including renal failure, encephalopathy coma) and death
- Severe VOD is associated with a high mortality rate of >80%

Predisposing Risk Factors:
- Regimen related
  - TBI, Gemtuzimab ozogamicin, melphalan, busulfan, carmustine, carmustine, cytarabine, actinomycin-D
  - Intensity of Conditioning
- Patient related
  - Age
  - Prior Liver Damage
  - Osteopetrosis, Neuroblastoma, Inherited Haemophagocytic Lymphohistiocytosis, CML.
  - Allogeneic HSCT (MUD)
  - Poor performance status

Cost:
- Supportive care estimated at €42K
- Recent data suggests VOD can quadruple HSCT costs

SCT at the edge of the next million

Did we reduce relapse incidence?

		Surv		TRM		RI	
		1980-1990	2000-2003	1980-1990	2000-2003	1980-1990	2000-2003
ALL		53%	61%	41%	30%	14%	22%
Stage	cP1	59%	70%	38%	21%	11%	13%
	AP	40%	47%	50%	30%	20%	21%
	BC	22%	16%	52%	50%	29%	38%
Donor type							
	HLA-id	55%	68%	38%	25%	14%	21%
	nid	35%	49%	57%	40%	14%	23%
	twin	73%	82%	10%	5%	46%	50%
	unrel	29%	53%	65%	37%	12%	14%
Score	0-1	54%	80%	31%	16%	13%	16%
	2-4	51%	60%	42%	32%	15%	22%
	> 4	25%	38%	62%	41%	15%	31%

Adapted from Gratwohl et al. Hematologica, 2006, vol 91(4) p513-521

SCT at the edge of the next million

Did we reduce relapse incidence?

Table 2. Comparison of Outcomes, Organ Dysfunction, Infection, and Acute GVHD after Transplantation between the Two Time Periods.*

Variable	1993–1997 (N=1418)	2003–2007 (N=1148)	All Patients		Patients Who Underwent Myeloablative Conditioning	
			Adjusted Hazard or Odds Ratio (95% CI)†	P Value	Adjusted Hazard or Odds Ratio (95% CI)†	P Value
	no. (%)					
Outcomes						
Death not preceded by relapse						
At day 200	419 (30)	186 (16)	0.40 (0.32–0.49)	<0.001	0.44 (0.36–0.54)	<0.001
Overall	580 (41)	297 (26)	0.48 (0.40–0.57)	<0.001	0.48 (0.40–0.58)	<0.001
Relapse or progression of a malignant condition	379 (27)	302 (26)	0.79 (0.66–0.94)	0.008	0.82 (0.68–0.99)	0.04
Death from any cause	891 (63)	545 (47)	0.59 (0.52–0.67)	<0.001	0.61 (0.53–0.69)	<0.001

Gooley et al, NEJM 2010

SCT at the edge of the next million

How can we reduce relapse incidence?

- ***Better scoring disease risk factors***
- ***Minimal residual disease determination***
- ***Donor cell chimerism determination***

SCT at the edge of the next million

Indication for SCT

Table 4 | Recommendations for allogeneic HSCT in patients with AML in their first complete remission based on integrated-risk profiles*

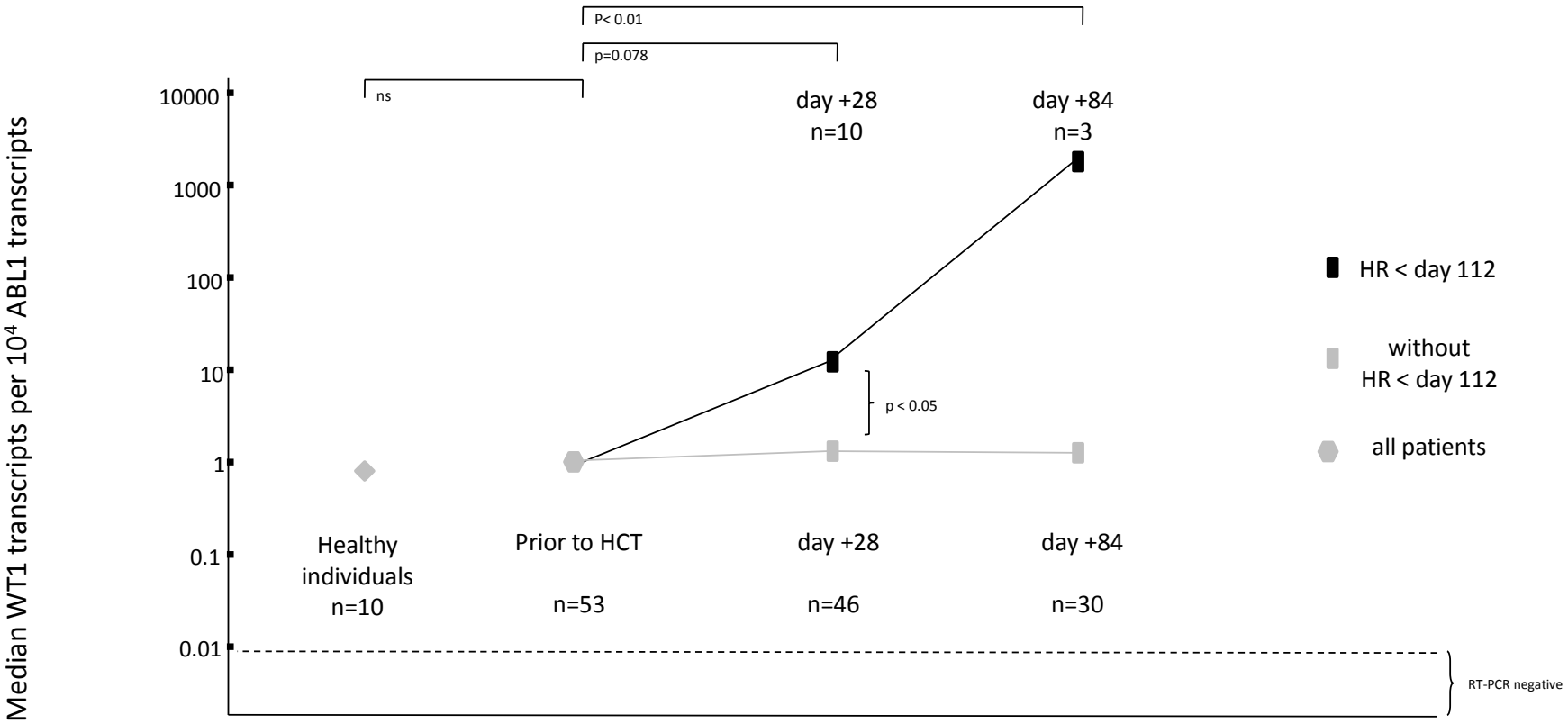
AML risk group‡	AML risk assessment§	Risk of relapse following consolidation approach		Prognostic scores for nonrelapse mortality that would indicate allogeneic HSCT as preferred consolidation		
		Chemotherapy or autologous HSCT (%)	Allogeneic HSCT (%)	EBMT score	HCT–CI score	Nonrelapse mortality risk (%)
Good	t(8;21) with WBC ≤20 Inv(16)/t(16;16) Mutated *CEBPA* (double allelic) Mutated NPM1 (No *FLT3*–ITD mutation) Early first complete remission and no MRD	35–40	15–20	NA (≤1)	NA (<1)	10–15
Intermediate	T(8;21) with WBC >20 Cytogenetically normal (or with loss of X and Y chromosomes), WBC count ≤100 and early first complete remission (after first cycle of chemotherapy)	50–55	20–25	≤2	≤2	<20–25
Poor	Otherwise good or intermediate, but no complete remission after first cycle of chemotherapy Cytogenetically normal and WBC >100 Cytogenetically abnormal	70–80	30–40	≤3–4	≤3–4	<30
Very poor	Monosomal karyotype Abn3q26 Enhanced Evi-1 expression	>90	40–50	≤5	≤5	<40

*The proposed patient-specific application of allogeneic HSCT in patients with AML in their first complete remission integrates the individual risks for relapse and nonrelapse mortality and aims for a DFS benefit of at least 10% for the individual patient compared with consolidation by a nonallogeneic HSCT approach. ‡The categorization of AML is based on cytogenetic, molecular and clinical parameters (including WBC) into good, intermediate and (very) poor subcategories and is subject to continuing study and debate. Here, categories are arbitrarily presented according to the latest policy of the Dutch–Belgian Cooperative Trial Group for Hematology Oncology and Swiss Group for Clinical Cancer Research (HOVON–SAKK) consortium.[144] Relapse percentages were derived from published reports.[5,15,20,35,40,50] §Includes response to first induction. Categorization requires one of the parameters indicated. Abbreviations: AML, acute myeloid leukaemia; EBMT, European Group For Blood and Marrow Transplantation; DFS, disease-free survival; Evi-1, Ecotropic viral integration site 1, HCT–CI, haematopoietic cell transplantation comorbidity index; HSCT, haematopoietic stem cell transplantation; *CEBPA*, gene encoding CCAAT enhancer-binding protein α; *FLT3*, gene encoding fms-like tyrosine kinase receptor-3; ITD, internal tandem duplication; NA, not advocated; *NMP1*, gene encoding nuclear matrix protein; MRD, minimal residual disease; WBC, white blood cell count.

Cornelissen et al., Nat. Rev. Clin. Oncol. 2012

SCT at the edge of the next million

WT1 transcript level to predict relapse



Lange et al, Leukemia 2011

SCT at the edge of the next million

How can we treat relapse?

- ***Detecting early hematological relapse***
- ***Tailoring immunosuppression***
- ***Donor cell chimerism determination***
- ***Donor lymphocyte infusion***

Molecular monitoring and management of relapse

DLI treatment

Table 2. Response of Chronic and Acute Leukemia to the Treatment With Donor Lymphocyte Transfusions

Diagnosis	No. of Patients		
	Studied	Evaluable*	Complete Remission (%)
CML			
Cytogen relapse	17	17	14 (82)
Hematologic relapse	53	50	39 (78)
Transformed phase	14	8	1 (12.5)
Polycythemia vera	1	1	1
AML	23	17	5 (29)
MDS	5	4	1 (25)
ALL	22	12	0
Total	135	109	61 (56)

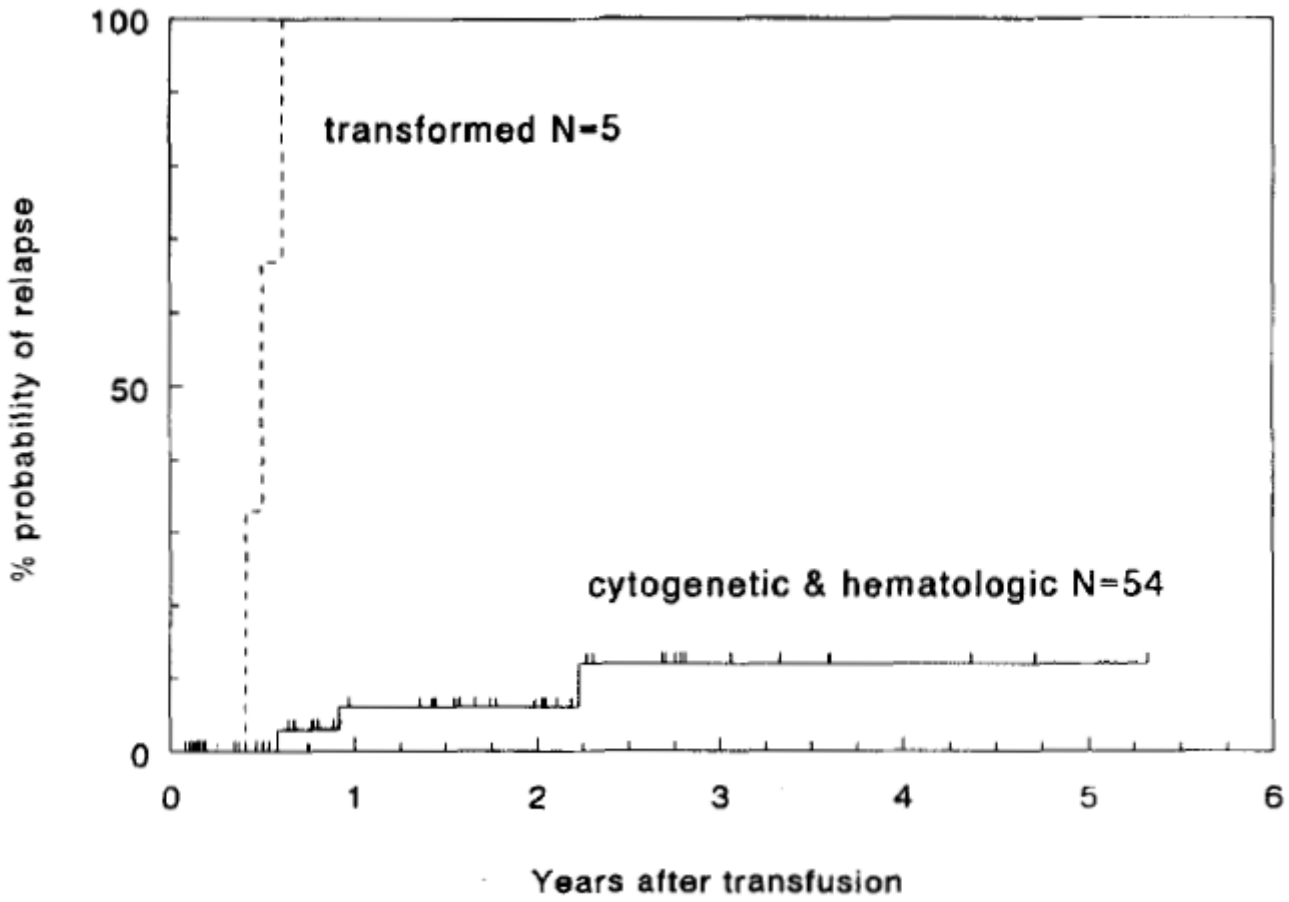
Fisher's exact test CML/polycythemia vera versus AML/MDS/ALL: $P < .000001$; CML cytogenetic/hematologic relapse versus transformed: $P = .0015$, AML/MDS versus ALL: $P = .049$.

*Patients in remission after chemotherapy and patients surviving less than 30 days after transfusion were excluded from evaluation.

Kolb et al, Blood 1995

Molecular monitoring and management of relapse

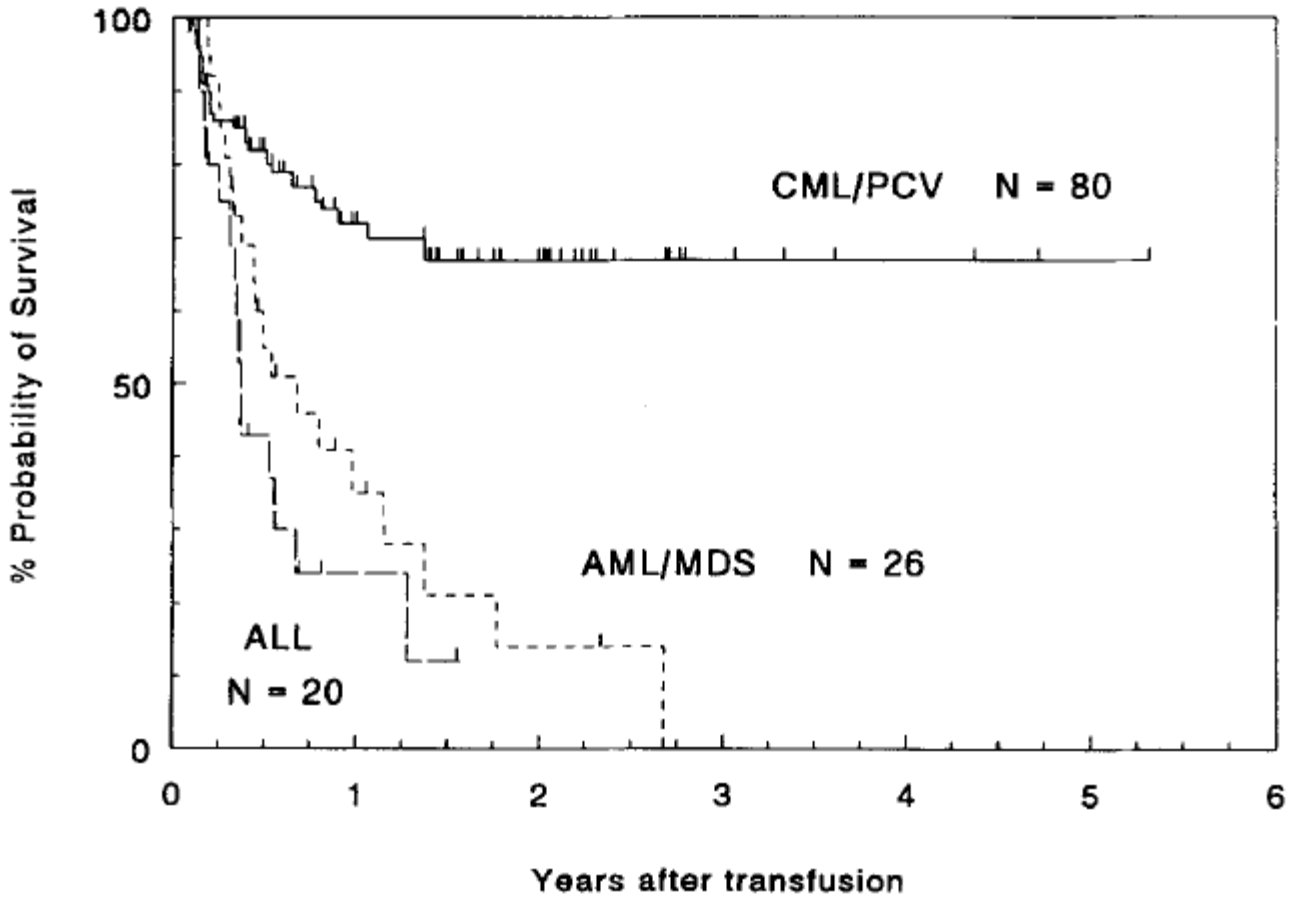
DLI treatment



Kolb et al, Blood 1995

Molecular monitoring and management of relapse

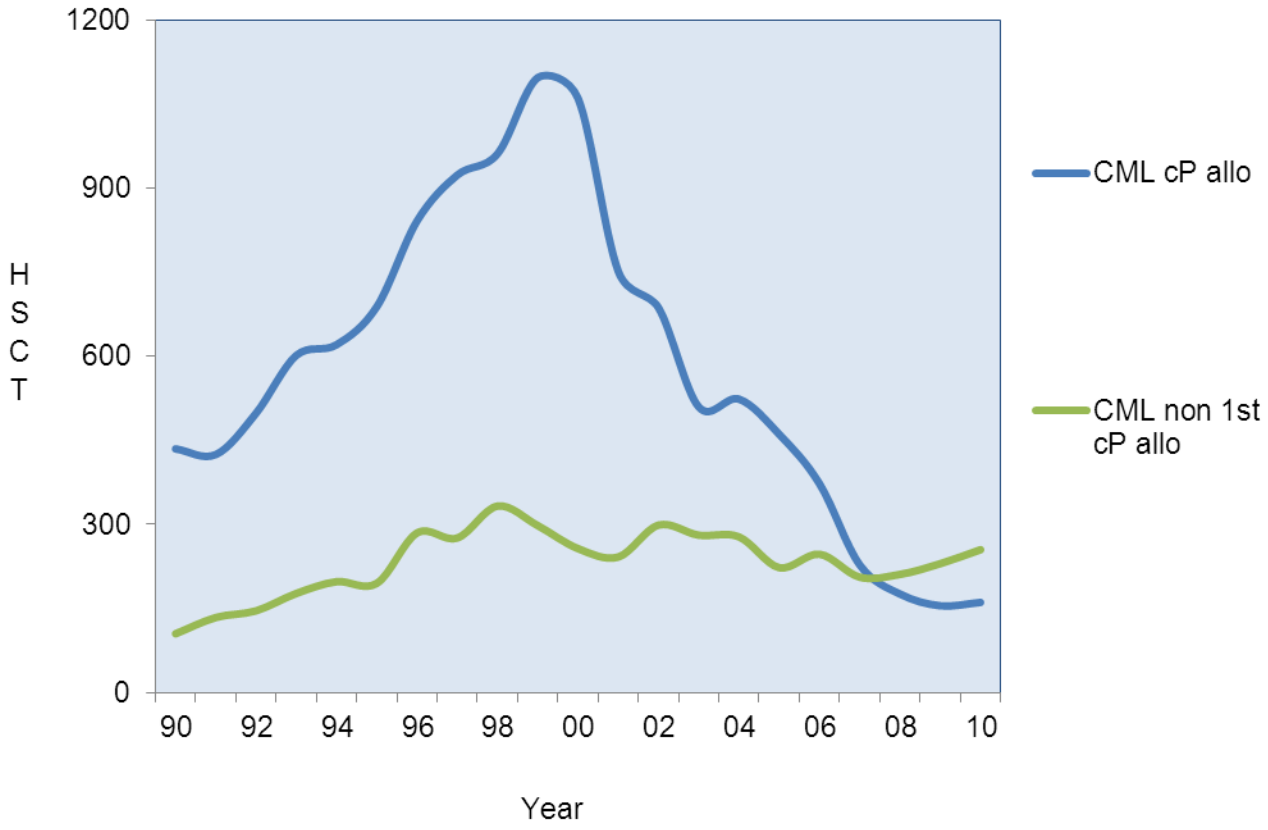
DLI treatment



Kolb et al, Blood 1995

EBMT Activity Survey 1990-2010:

changes in HSCT for CML



Effect of imatinib on transplantation for CML

Complications after Stem Cell Transplantation

Conclusions

NRM decreased continuously in the last decades

infectious complications have changed

veno-occlusive-disease might develop to severe complication with high mortality.

molecular marker increasingly important not only for prediction and monitoring but also for treatment indication

Timing for stem cell transplantation essential for relapse reduction