Hemostasia y cancer
Saturday 27 Sep 10:00

Hemostasis and Cancer

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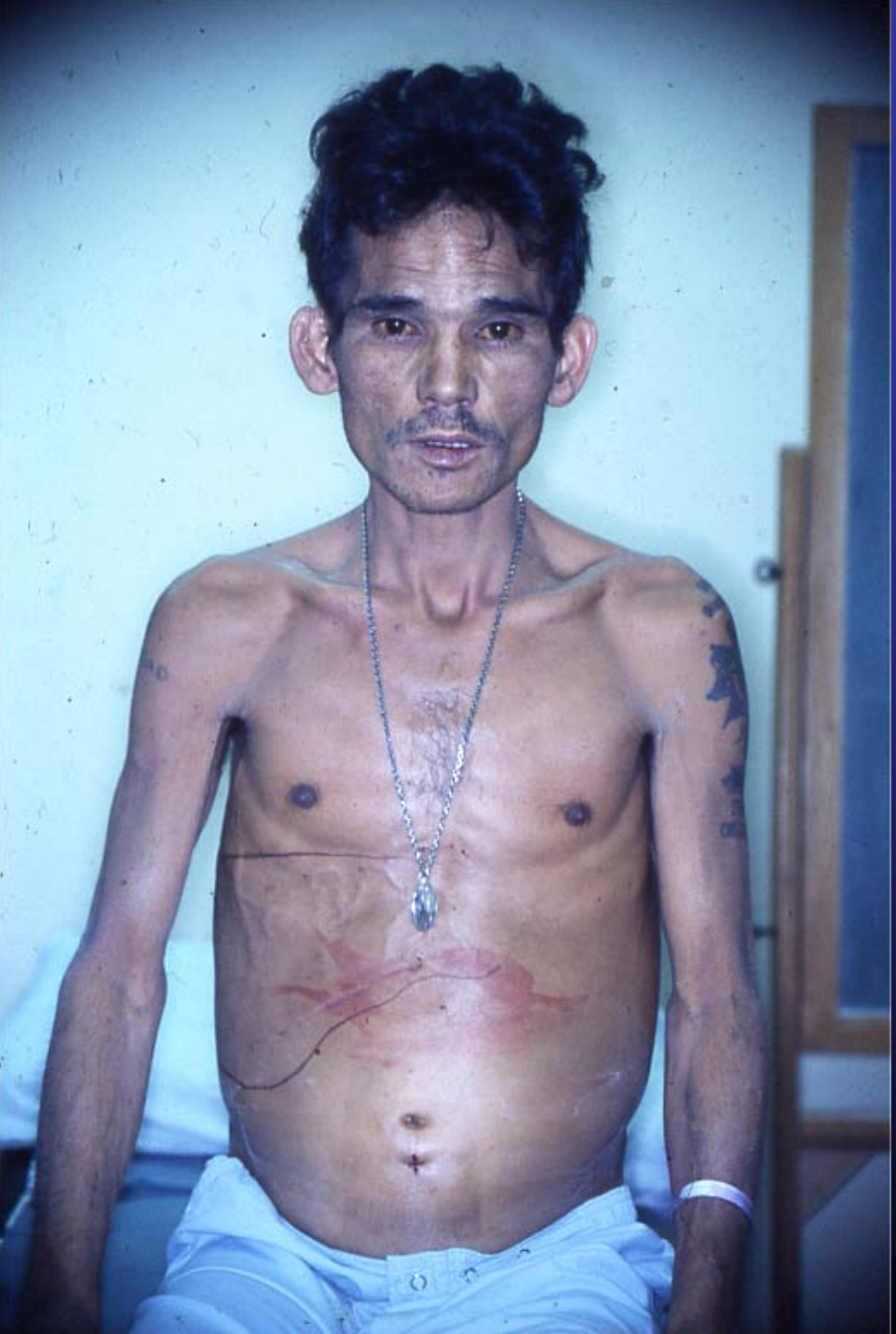
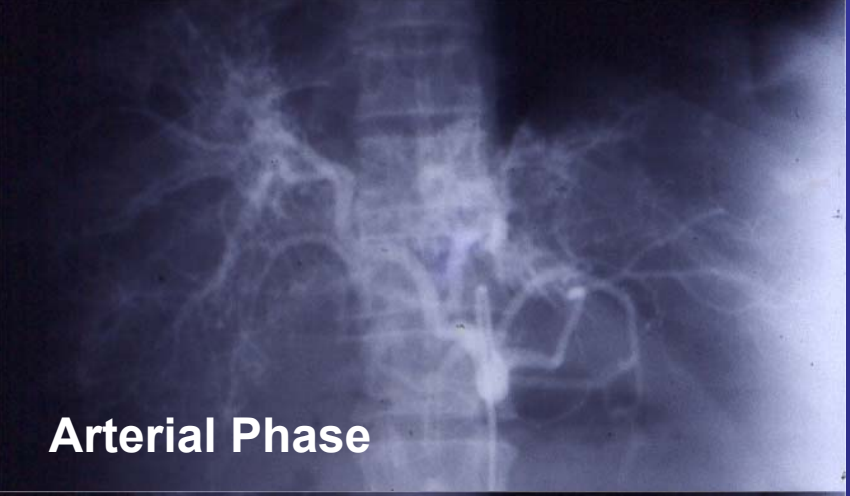
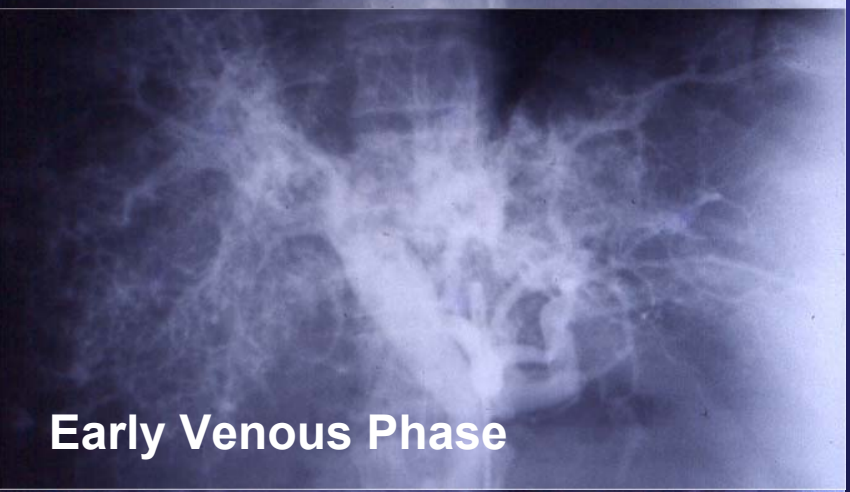
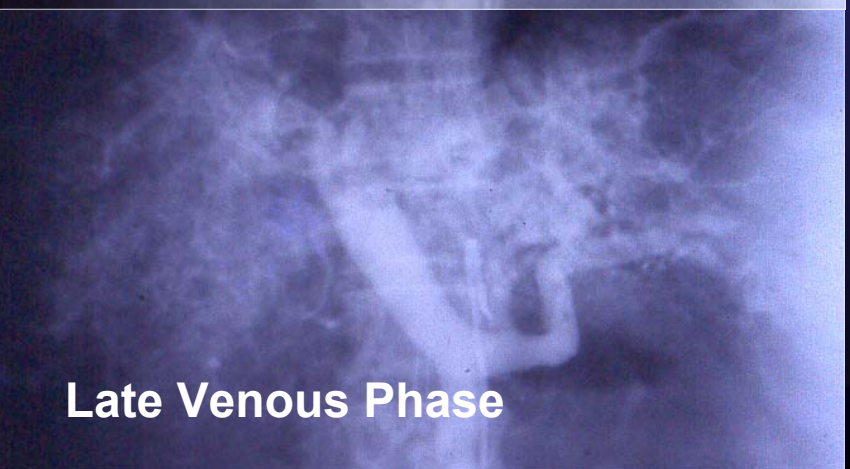


A 42 yo Filipino merchant seaman with a history of IV drug abuse and alcoholism came to the hospital with:

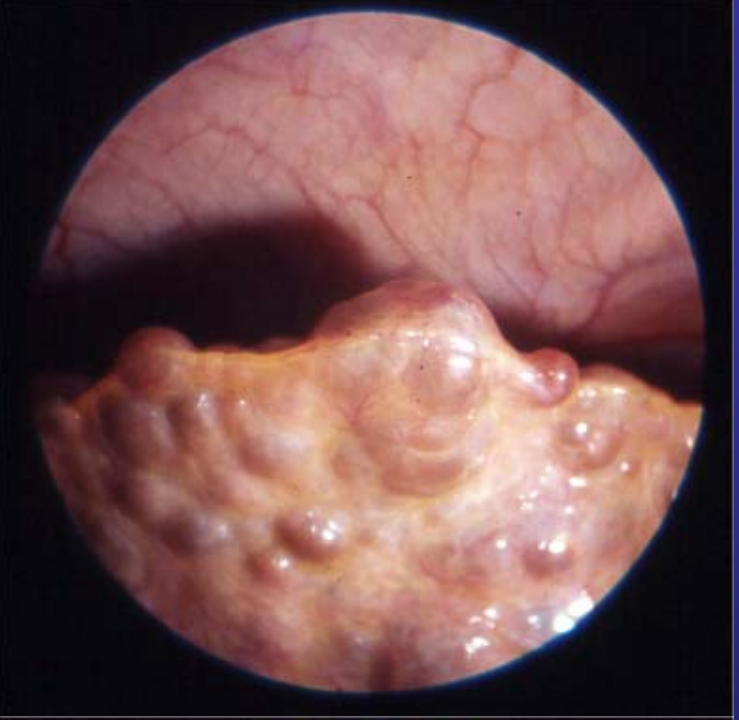
- Cachexia
- Jaundice
- Ascites
- Hepatomegally
- Venous distention over his upper abdomen

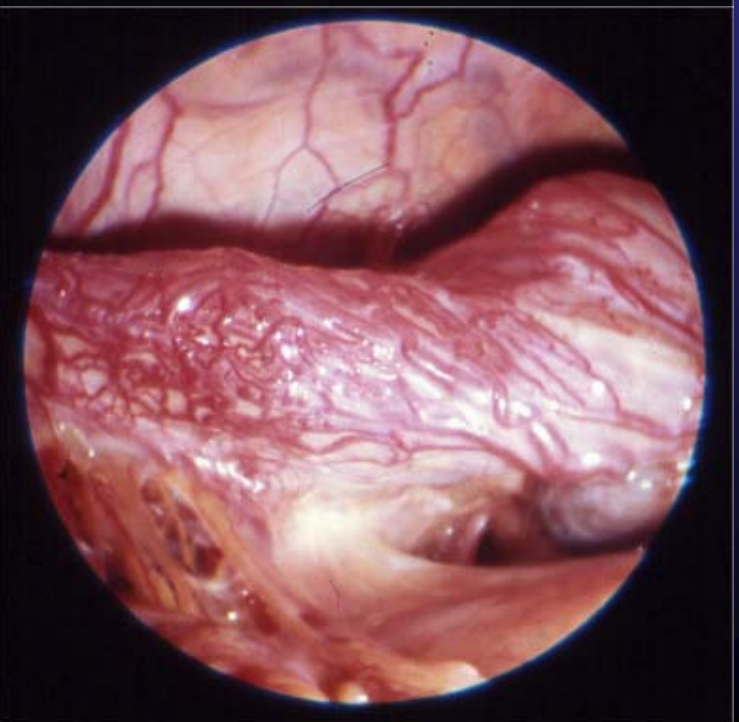




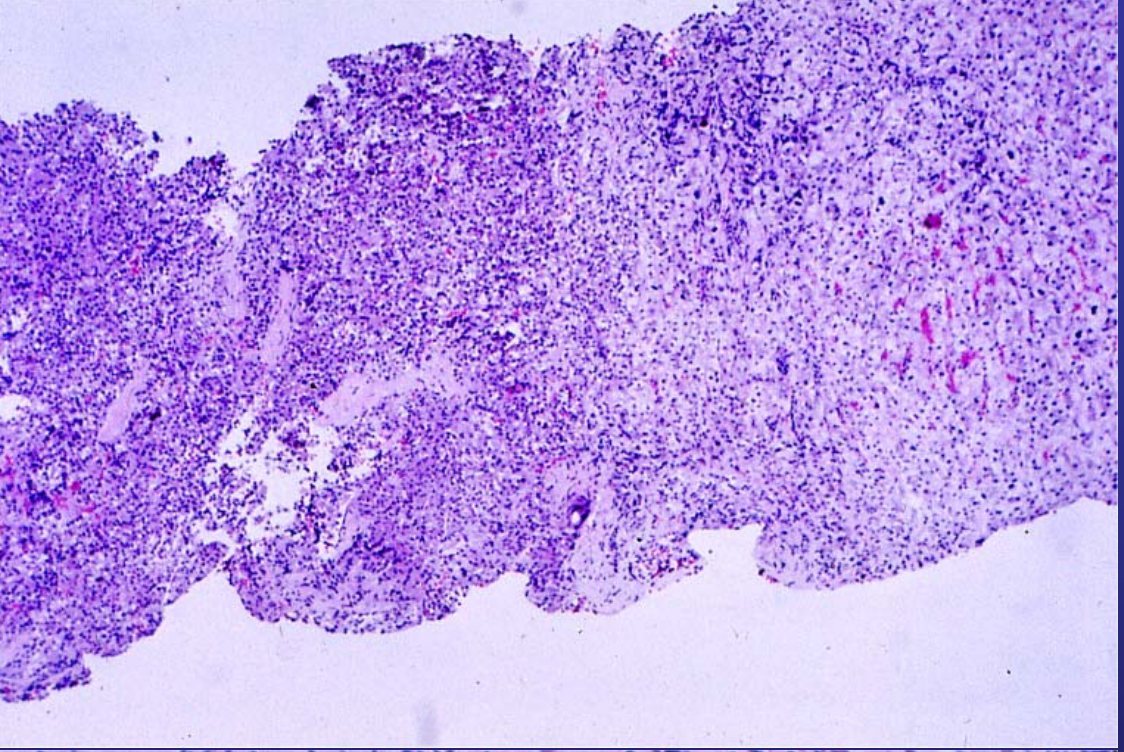


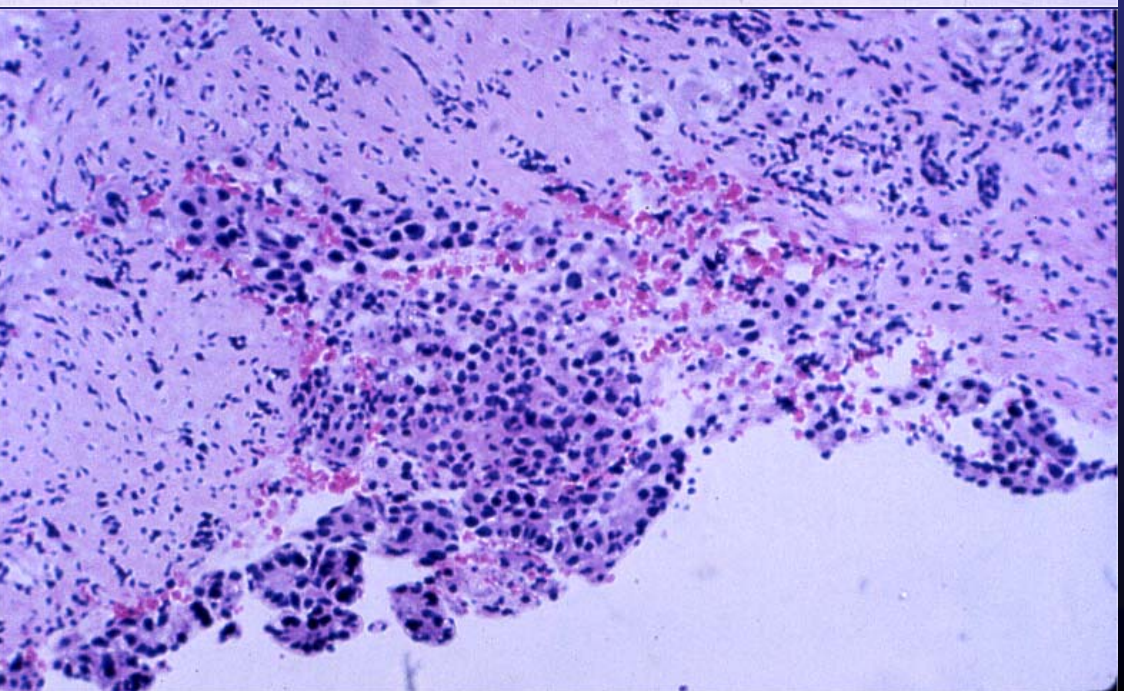
Arteriogram revealed marked vascular distortion with prunning of vessels and tumor blush. Even before arteriolar and capillary filling took place there was marked portal venous reflux into the splenic vein and esophageal varices



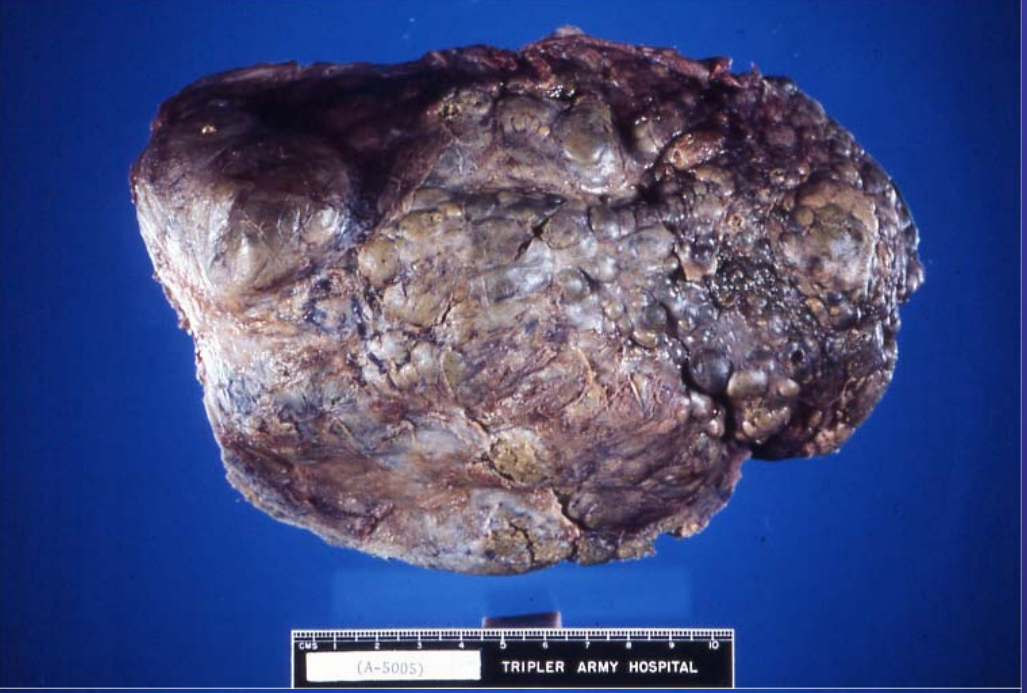


Peritonioscopy was preformed after his INR was lowered from 2.9 to 1.5 with 6 units of plasma. Peritonioscopy revealed a large nodular liver with tortuous vessels and marked vascular congestion of the falciform ligament and abdominal wall.





Liver biopsy showed obliteration of normal liver architecture with fibrosis, nodules, and clusters of hyperchromic cells compatible with hepatocellular carcinoma.



The patient died four days after biopsy of hematemesis from ruptured esophageal varices. On the morning he died, his INR was 2.7. At autopsy his liver was largely replaced by tumor.

Cancer and Hemostasis

- Cancer causes bleeding
- Bleeding as a sign of cancer
- Thrombosis as a sign of cancer
- Current recommendations for platelet use in leukemia and diagnostic procedures
- Current recommendations for plasma use in diagnostic procedures
- Current recommendations for anticoagulation in cancer

Bleeding as a sign of cancer

- Respiratory tract bleeding
- Gastrointestinal bleeding
- Urinary tract bleeding
- Vaginal bleeding
- Bleeding into the skin
- Skin lesions that bleed

- All of these symptoms must be evaluated as possible Sx of cancer

Clotting as a sign of cancer Trousseau's Syndrome

- Cancer associated thrombosis
  - Described by Armand Trousseau in 1865
  - Trousseau later diagnosed it in himself
- Inapparent cancer can trigger thrombosis
  - Illryd James and Matheson in 1935

  - A nickles worth of cancer (can give a dollar's worth of clot). Deborah Ornstein Ann Int Med 2008 Sep; 149 250-352.

Cancer Screening in Patients with Venous Thromboembolism

Carrier et al., Ann Int Med 2008 Sep; 149:323-333

- Unprovoked VTE is associated with a 6% incidence of cancer at diagnosis and a 10% incidence over 12 months.
- Provoked VTE only has a 2% risk,
- The harder you look, the more cancers you find. Abdominal and pelvic CT is most sensitive test.
- Not clear that finding cancer early improves outcome.

Cancer as a cause of bleeding

- Low platelets
  - Lymphoid malignancy related ITP
    - CLL, Hodgkin's, LGL proliferation,
  - Chemotherapy related thrombocytopenia from bone marrow suppression
  - Chemotherapy related thrombocytopenia from thrombotic microangiopathies with wet purpura
  - Drug related (heparin in catheters)
  - Alloimmunization, post transfusion purpura

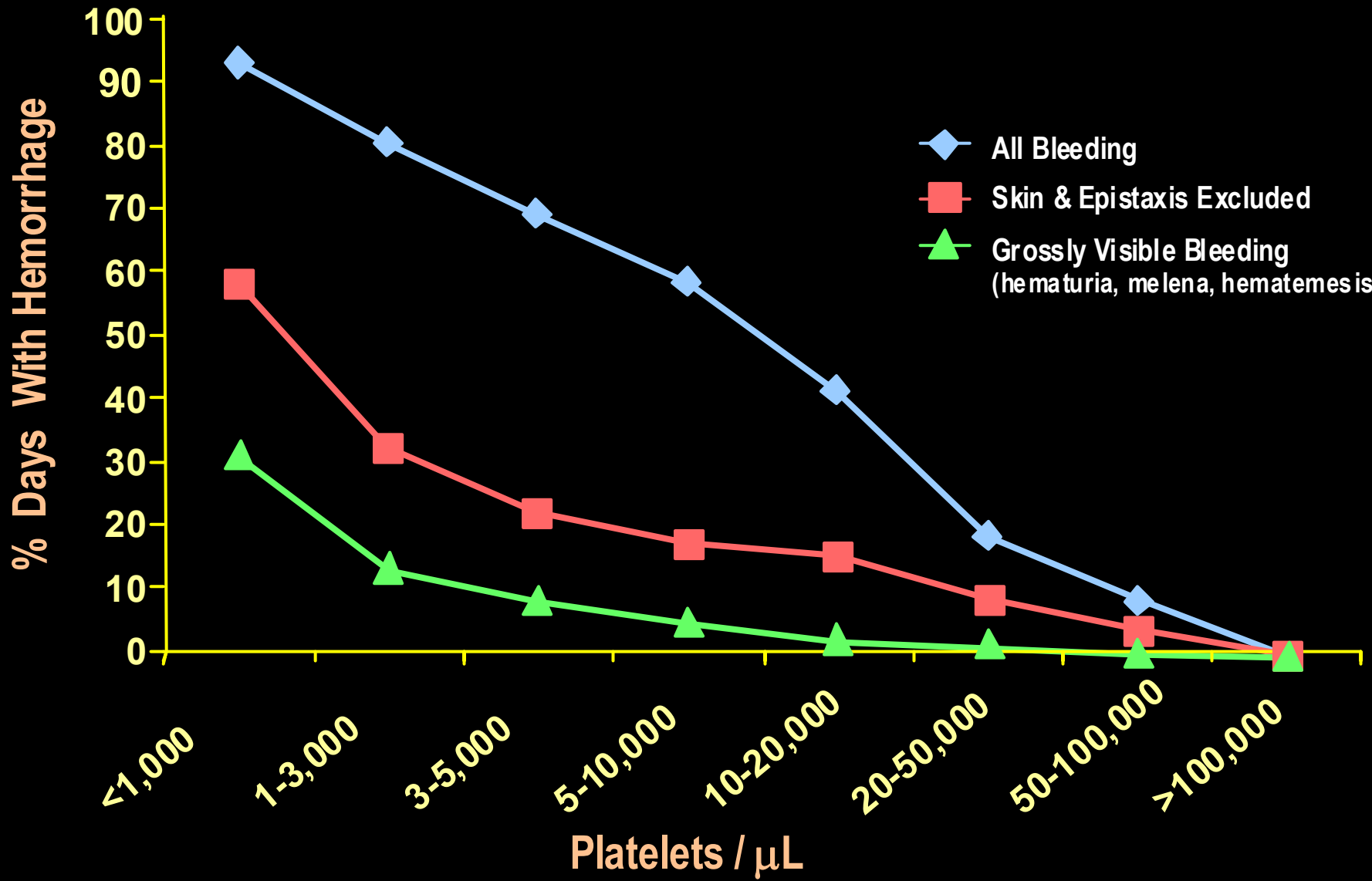
Cancer as a cause of bleeding

- Prolonged coagulation times
  - Antibiotic-related Vit K deficiency
  - Liver dysfunction from
    - Metastases
    - Drugs
    - Radiation
  - Microangiopathic factor consumption on damaged endothelium from high-dose chemotherapy or radiation
  - Asparagase consuming fibrinogen

What do we know about platelet therapy in leukemia?

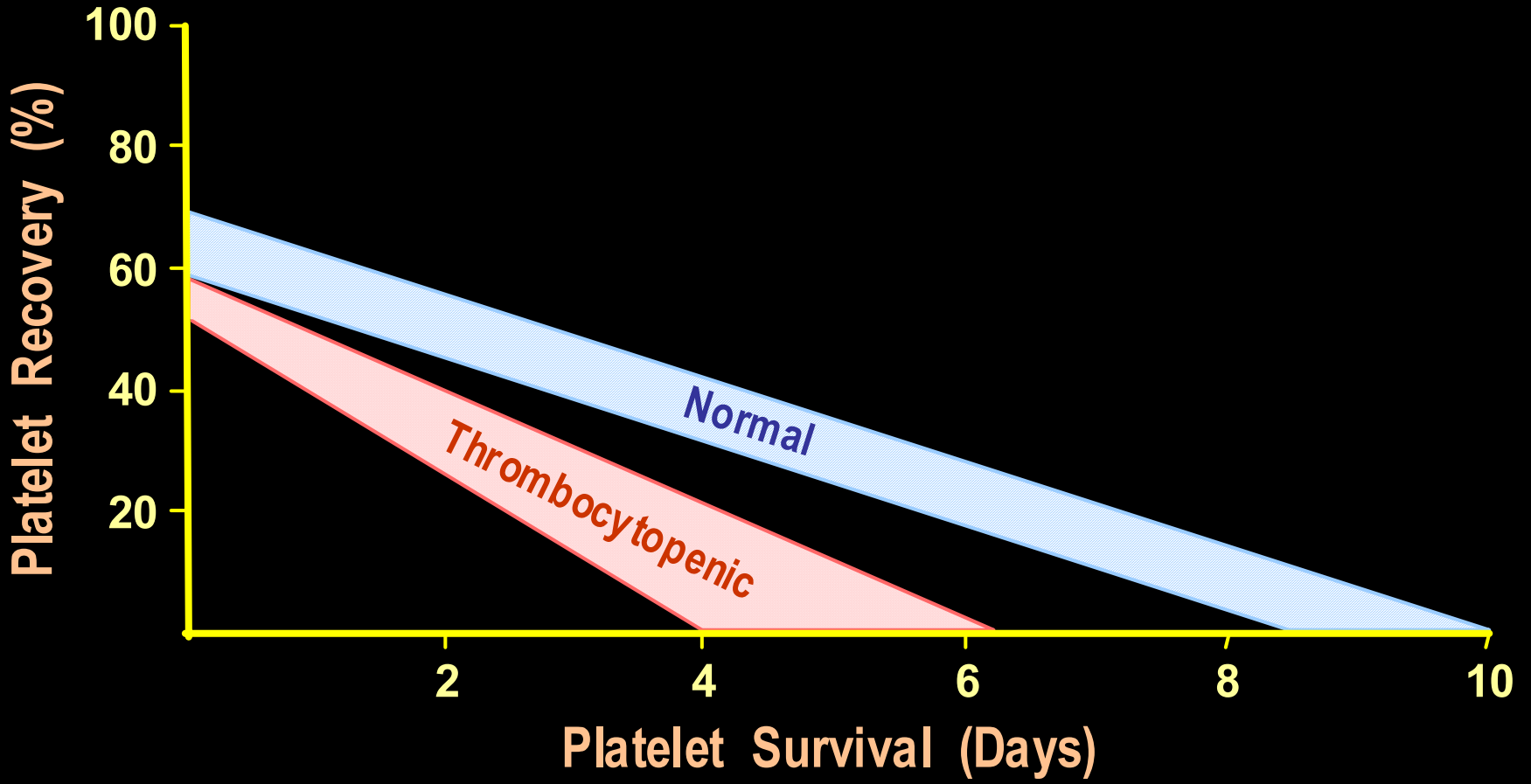
- We know that patients get thrombocytopenic.
- We know that transfusing platelets raises platelet counts and prevents bleeding and mortality.
- We know that some patients get refractory to platelet transfusions.
- We have prospective data on the safety of transfusion triggers.
- We know that leukoreduction reduces alloimmunization and febrile reactions.

RELATIONSHIP BETWEEN PLATELET COUNT AND HEMORRHAGE

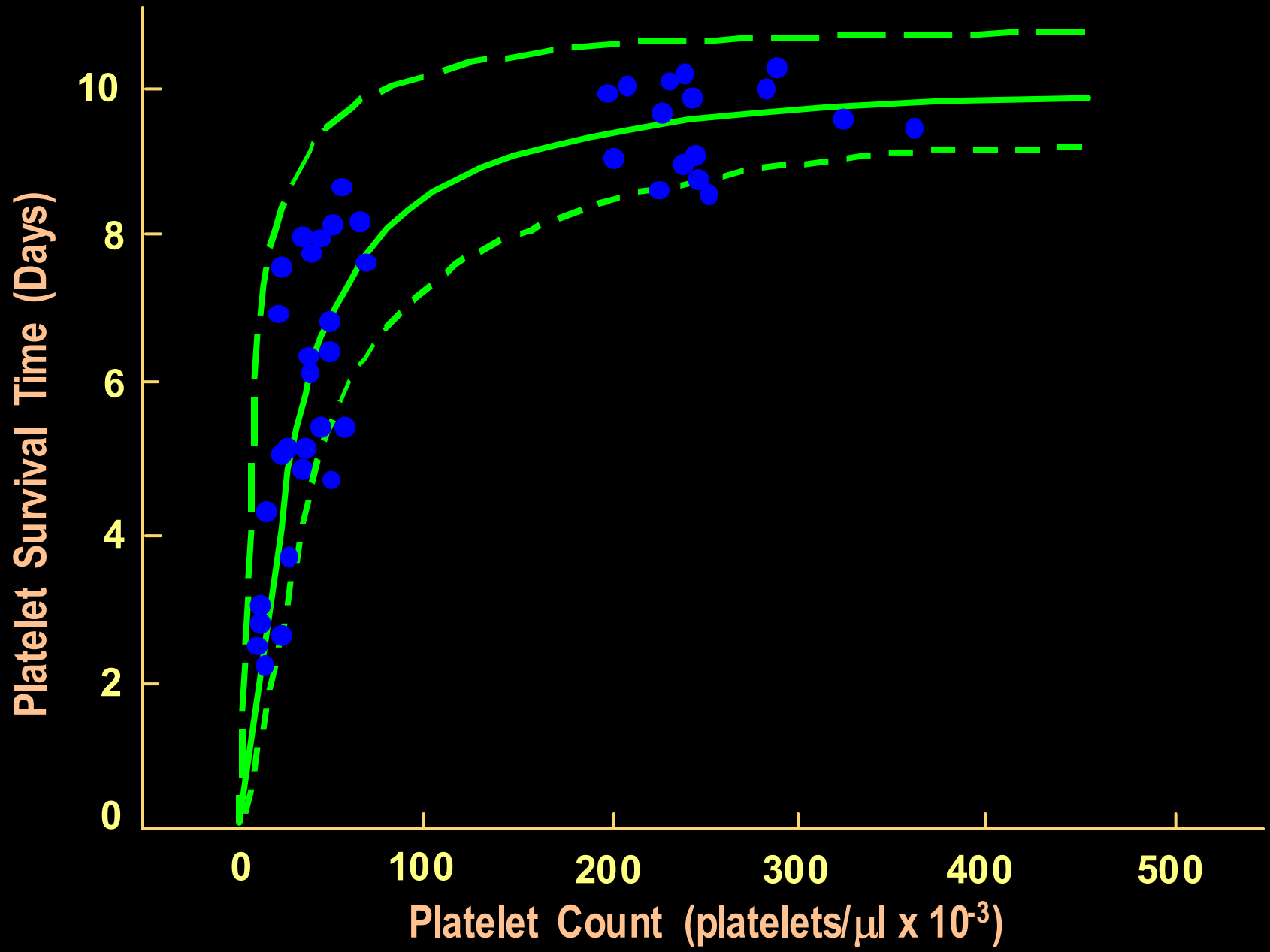


Gaydos, *et al.*; *NEJM* 1962;266:905.

PLATELET RECOVERY AND SURVIVAL IN NORMALS AND THROMBOCYTOPENIC PATIENTS



Slichter & Harker; *Clin Hematology* **7:523, 1978.**



Hanson & Slichter; *Blood* 56:1105, 1985.

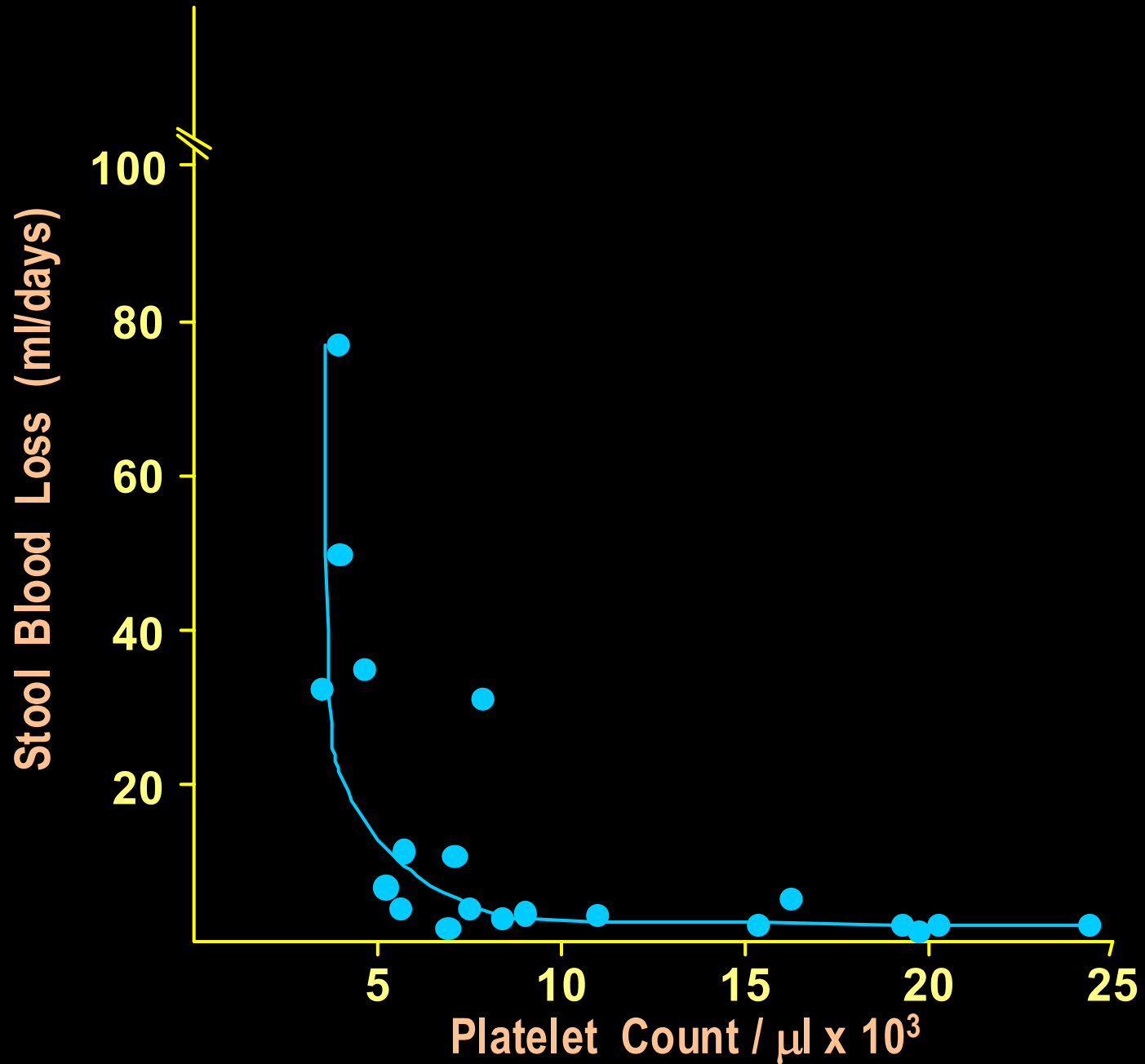
LOSS OF PLATELETS

Platelets are lost from circulation by two mechanisms:

- Senescence: platelet removal by the reticuloendothelial system.
  - Maximum platelet lifespan - 10.3 days
- Random: platelet loss in hemostasis (endothelial support)
  - 7,100 platelets/μl per day

NUMBER OF PLATELETS REQUIRED TO SUPPORT THE ENDOTHELIUM

- 70 kilo man assumed to have a blood volume of 5 L.
- Needs 7.1×10^9 platelets/L/day.
- Therefore, $5 \times 7.1 \times 10^9 = 3.6 \times 10^{10}$ platelets/day.
- To account for splenic pooling, requirement = 5.4×10^{10}.
- One platelet concentrate contains, on average, 8.3×10^{10} platelets.



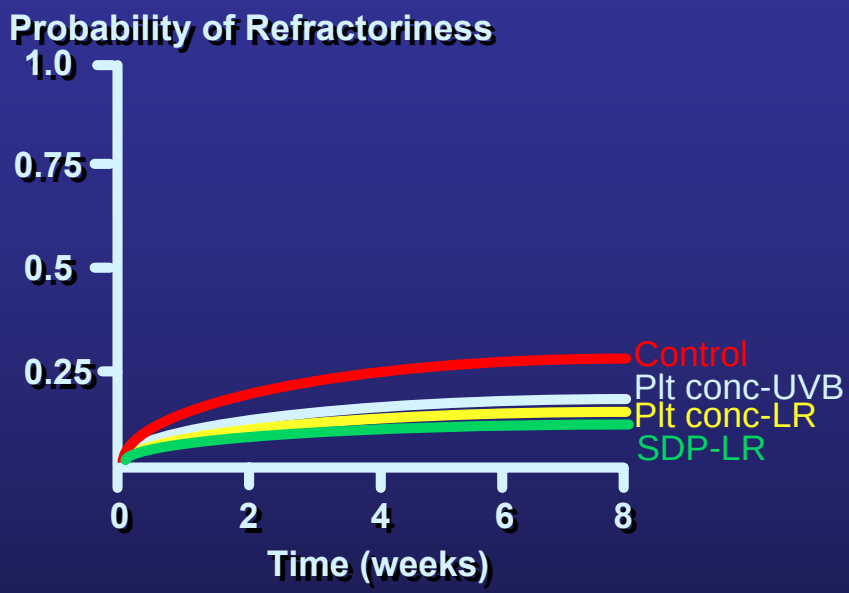
Slichter & Harker, *Clin Haematol* 1978;7:523.

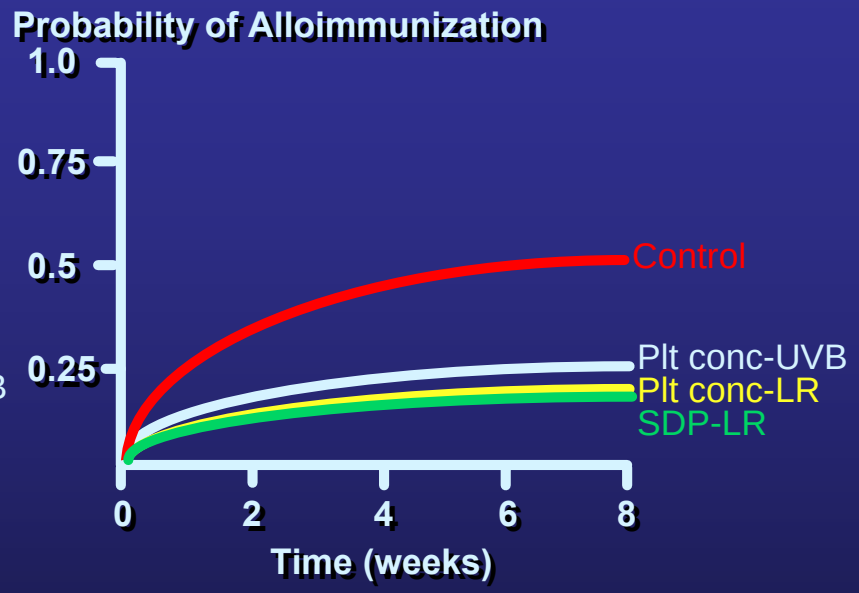
How many platelets for an LP?

- Howard et al. JAMA 2000 - reviewed 5223 LPs on 958 consecutive children with ALL at St. Jude's. No serious complications.
- 742 LPs at 20-50K
- 170 LPs at 10-20K
- 29 LPs at <10K

- New Dutch guideline >40K for LP

Trial to Reduce Alloimmunization to Platelets





Summary of results:

- all treatment groups had significantly less HLA alloimmunization and refractoriness than the control group
- no differences between study groups
- low incidence of bleeding (0-1%) in all groups
- filtered components recommended for AML patients

TRAP Trial Study Group. *NEJM* 1997;337:1861-9.

How do we prescribe platelet products?

- What product – leukocyte-reduced, single donor apheresis platelets if possible.
- When (at what transfusion trigger)?
  - With no bleeding – 5K, 10K, 20K
  - For procedures – 20K, 50K, 100K
  - For active bleeding
- How much (1U, 3U, 6U, 10U)?

EFFECTS OF PLATELET DOSE ON TRANSFUSION RESPONSES

	Medium Dose ($4\text{-}6 \times 10^{11}$)	High Dose ($6\text{-}8 \times 10^{11}$)	Very High Dose ($>8 \times 10^{11}$)
Platelets Transfused ($\times 10^{11}$)	4.6 ± 0.6	6.5 ± 0.5	8.9 ± 0.7
Pre-Transfusion Platelet Count/μl	19,000	22,000	21,000
Platelet Increment	$33{,}000 \pm 22{,}000$	$51{,}000 \pm 29{,}000$*	$62{,}000 \pm 34{,}000$*
Transfusion-Free Interval	2.6 ± 0.7	3.3 ± 1.2*	4.1 ± 1.4*

*$p<0.01$ compared to next lower dose.

Data based on 69 patients who received all 3 doses of "fresh" platelets. Order of transfusions based on availability of one of the doses.

Norol, *et al.*; *Blood* 92:1448, 1998.

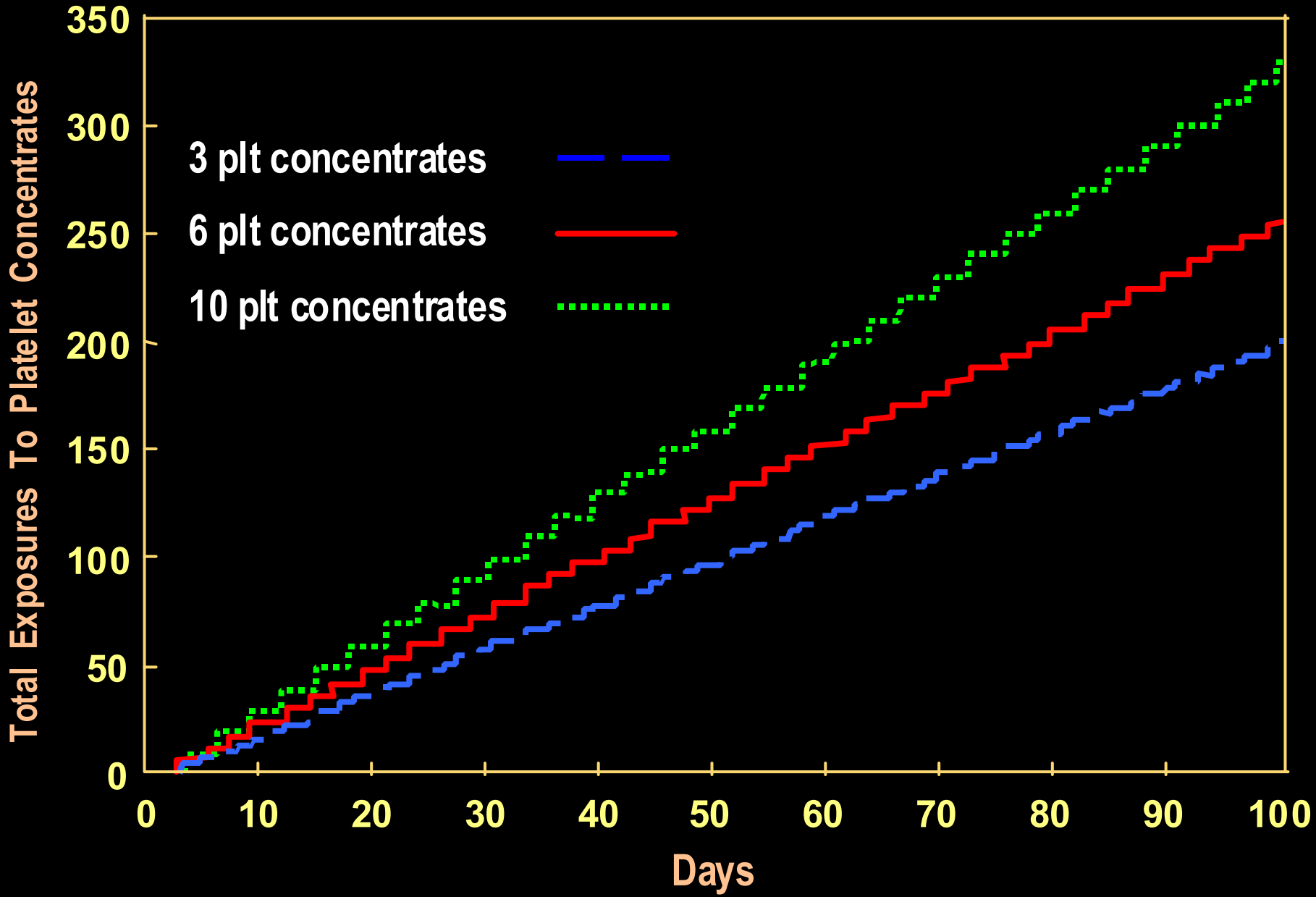
POST-TRANSFUSION RESPONSES TO LOW *versus* HIGH DOSE PLATELET TRANSFUSIONS

	Low Dose	High Dose	*P*
Product Platelet Count x 10^{11}*	3.1	5.0	
Pre-Transfusion Platelet Count/μl	11,000	11,000	0.99
Platelet Increment/μl	17,000	31,000	<0.0001
Transfusion-Free Interval (Days)	2.2	3.0	<0.01

*Pre-filtration platelet counts.

Data based on 79 paired prophylactic platelet transfusions given to 46 thrombocytopenic patients.

Klump, *et al.*; *Transfusion* 39:674, 1999.



Hersh, *et al.*; *Transfusion* 38:637, 1998.

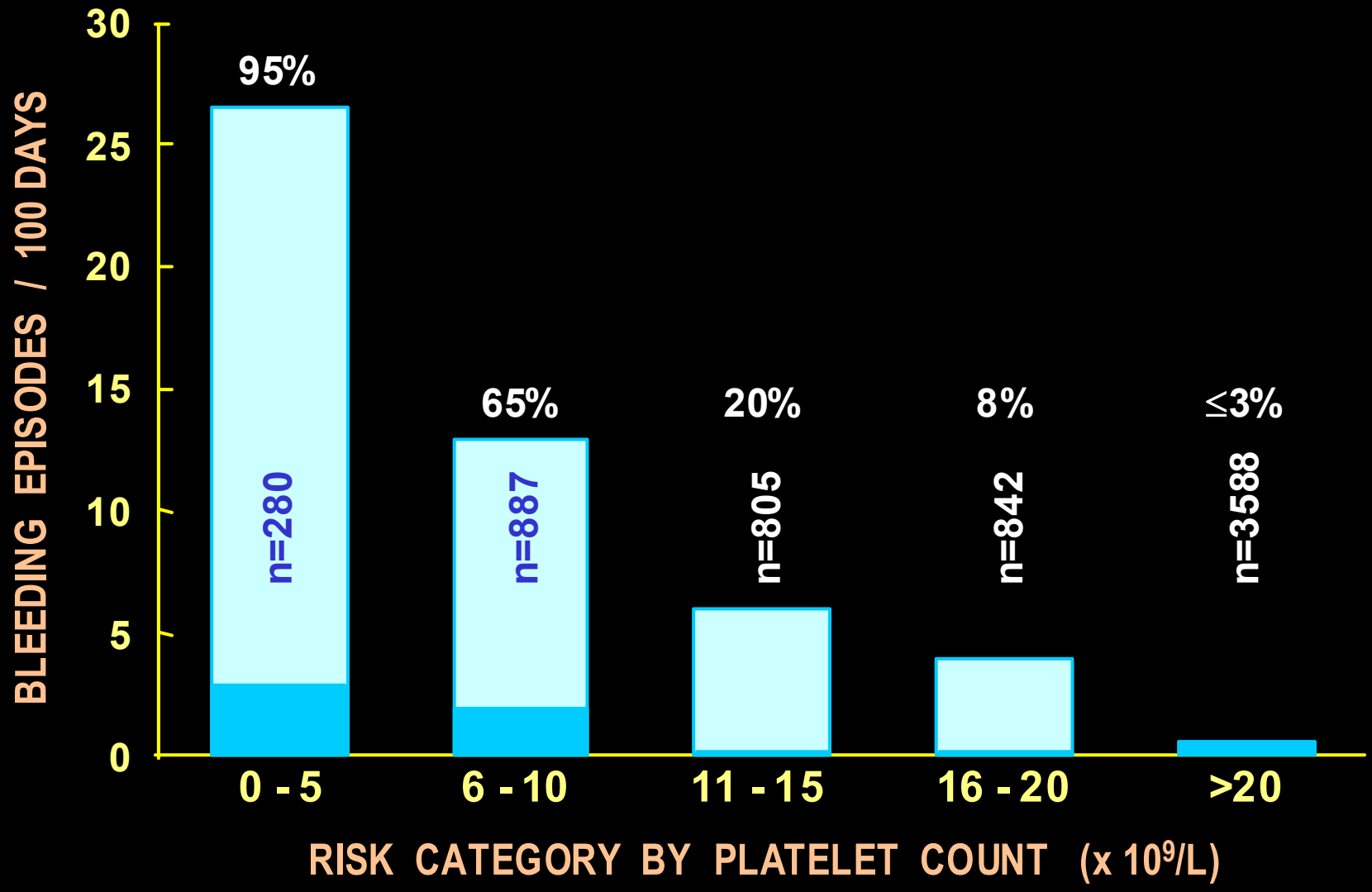
PLATELET TRANSFUSION TRIALS COMPARING PROPHYLACTIC PLATELET TRANSFUSION "TRIGGERS" OF 10,000 PLATELETS/μL *VERSUS* 20,000 PLATELETS/μL

	10,000/μL PLATELET TRANSFUSION TRIGGER			20,000/μL PLATELET TRANSFUSION TRIGGER		
First Author	Number Of Patients	Major Bleeding (%)*	Hemorrhagic Deaths	Number Of Patients	Major Bleeding (%)*	Hemorrhagic Deaths
Rebulla, 1997	53	22	1	52	20	0
Heckman, 1997	37		0	41		0
Zumberg, 2002	78	14	0	81	17	0
Gil-Fernandez, 1996	103	12	3	87	14	4
Wandt, 1998	58	18	0	47	17	0
Navarro, 1998	21	42	0	27	30	0
Lawrence, 2001	77	15		64	18	

*Major bleeding generally indicates bleeding requiring red cell transfusions.

WORLD HEALTH ORGANIZATION (WHO) BLEEDING GRADES

Score	Type of Bleeding
0	None.
1	Petechiae, ecchymosis, occult blood in body secretions, mild vaginal spotting.
2	Evidence of gross hemorrhage not requiring red blood cell transfusion over routine transfusion needs; e.g. epistaxis, hematuria, hematemesis.
3	Hemorrhage requiring transfusion of 1 or more units of RBC / day.
4	Life-threatening hemorrhage, defined as either massive bleeding causing hemodynamic compromise or bleeding into a vital organ (e.g., intracranial, pericardial, or pulmonary hemorrhage).



Gmur, *et al.*, *Lancet* 1991;338:1223.

PLATELET TRANSFUSION PROTOCOL

Morning Platelet Count ($\times 10^9$/L)	Prophylactic Platelet Transfusion Given
0 - 5	In every case.
6 - 10	In the presence of: 1) Fresh minor hemorrhagic manifestations 2) Body temperature >38.0°C.
11 - 20	In the presence of: 1) Coagulation disorders and/or heparin therapy. 2) Before bone-marrow biopsy or lumbar puncture.
>20	In the presence and until control of: 1) Major bleeding complications. 2) Before minor surgical procedures (other biopsies). 3) Before central venous catheter insertion or arterial punctures.

Gmur, *et al.*, *Lancet* 1991;338:1223.

PROPHYLACTIC PLATELET TRANSFUSION TRIGGER TRIAL

RANDOMIZATION

Patients were randomly assigned to receive prophylactic platelet transfusions (6 pooled random donor platelet concentrates stored for 4 to 5 days) for morning platelet counts of 5,000/μl, 10,000/μl, or 20,000/μl.

Slichter SJ, *et al*., *Blood* 94(Suppl 1):376a, 1999.

DETERMINATION OF RADIOCHROMIUM-LABELED STOOL BLOOD LOSS

- Patients had an aliquot of their RBC's labeled with ^{51}Chromium.
- All stools and a 5 ml daily blood sample were analyzed for radioactivity.

Slichter SJ, *et al*., *Blood* 94(Suppl 1):376a, 1999.

DEMOGRAPHIC DATA

Patients	85	
Female	58	(68%)
Diagnosis:		
Breast Cancer	38	(45%)
AML	28	(33%)
NHL	9	(11%)
ALL	3	(4%)
Multiple Myeloma	3	(4%)
Hodgkin's	2	(2%)
Ovarian Cancer	2	(2%)
Treatment:		
Chemotherapy	61	(72%)
PBSCT	24	(28%)

Slichter SJ, *et al*., *Blood* 94(Suppl 1):376a, 1999.

STOOL BLOOD LOSS

Transfusion Trigger	Patients	Stool Blood Loss (mls) Total	Stool Blood Loss (mls) Loss Per Thrombocytopenic Day*
5,000/μL	31	111 ± 29	11 ± 2
10,000/μL	26	71 ± 15	6 ± 1
20,000/μL	24	136 ± 53	10 ± 3

Data reported as average ±1 S.E.

*Total stool blood loss divided by number of days platelet count ≤20,000/μL.

Slichter SJ, *et al*., *Blood* 94(Suppl 1):376a, 1999.

PLATELET TRANSFUSIONS

Transfusion Trigger	Patients	Thrombocytopenic Days*	Transfusions	
			Total	Per Day
5,000/μL	31	9	2.0	0.25
10,000/μL	26	11	3.5	0.35
20,000/μL	24	10	5.0	0.58

p=0.03

p=0.001

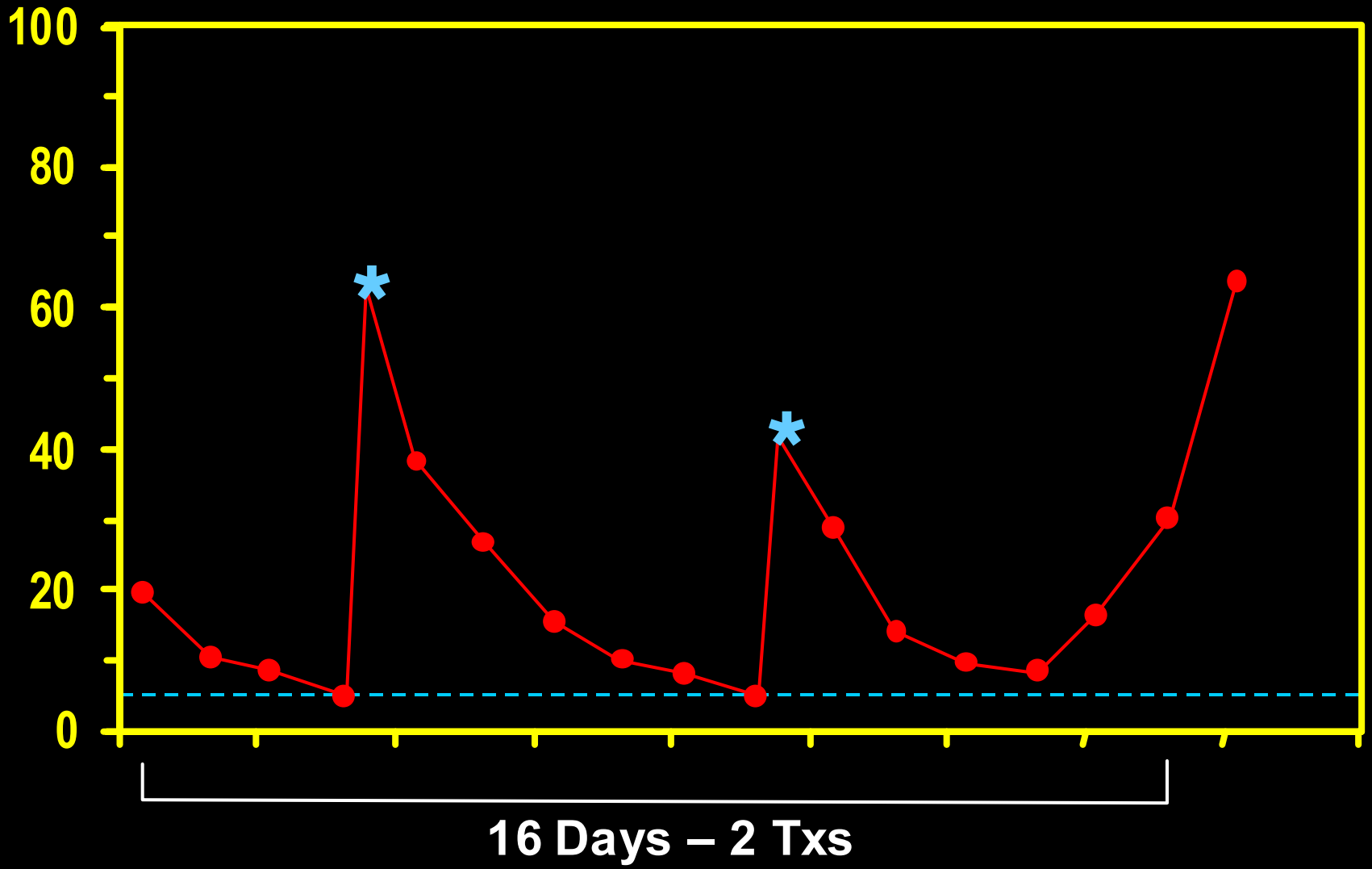
p=0.04

p=0.001

*Days platelet count ≤20,000/μL for each study arm.
Data reported as median.

Slichter SJ, *et al*., *Blood* 94(Suppl 1):376a, 1999.

AML Platelet Trigger Trial - 5,000/μl Arm



Slichter SJ, *et al*., *Blood* 94(Suppl 1):376a, 1999.

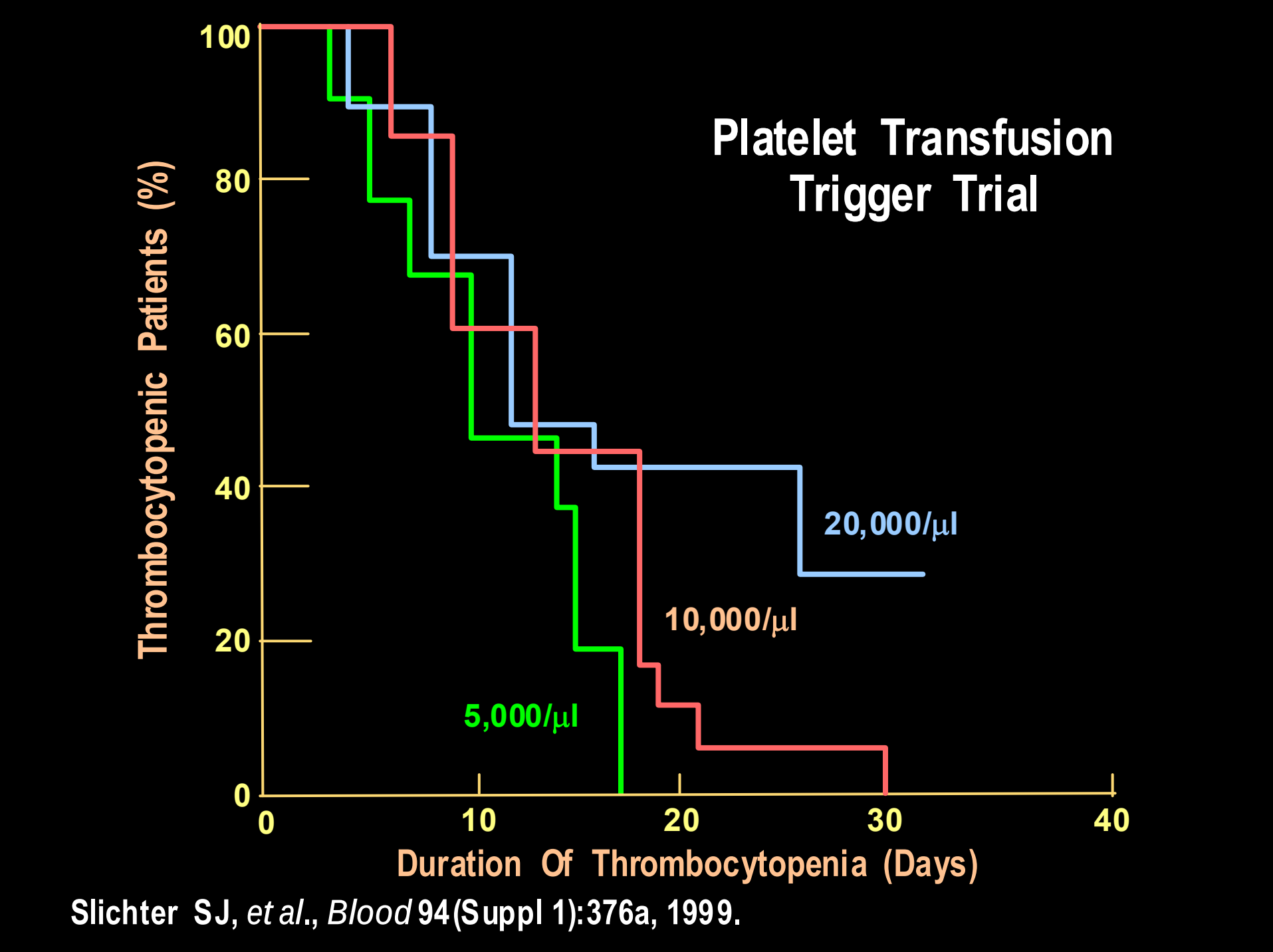
RBC TRANSFUSIONS

Transfusion Trigger	Patients	RBC Transfusions	
		Total	Loss Per Thrombocytopenic Day*
5,000/μL	31	4.1 ± 0.6	0.4 ± 0.04
10,000/μL	26	4.8 ± 0.7	0.4 ± 0.04
20,000/μL	24	5.5 ± 1.0	0.4 ± 0.05

Data reported as average ±1 S.E.

*Total red cell transfusions divided by number of days platelet count ≤20,000/μL.

Slichter SJ, *et al*., *Blood* 94(Suppl 1):376a, 1999.



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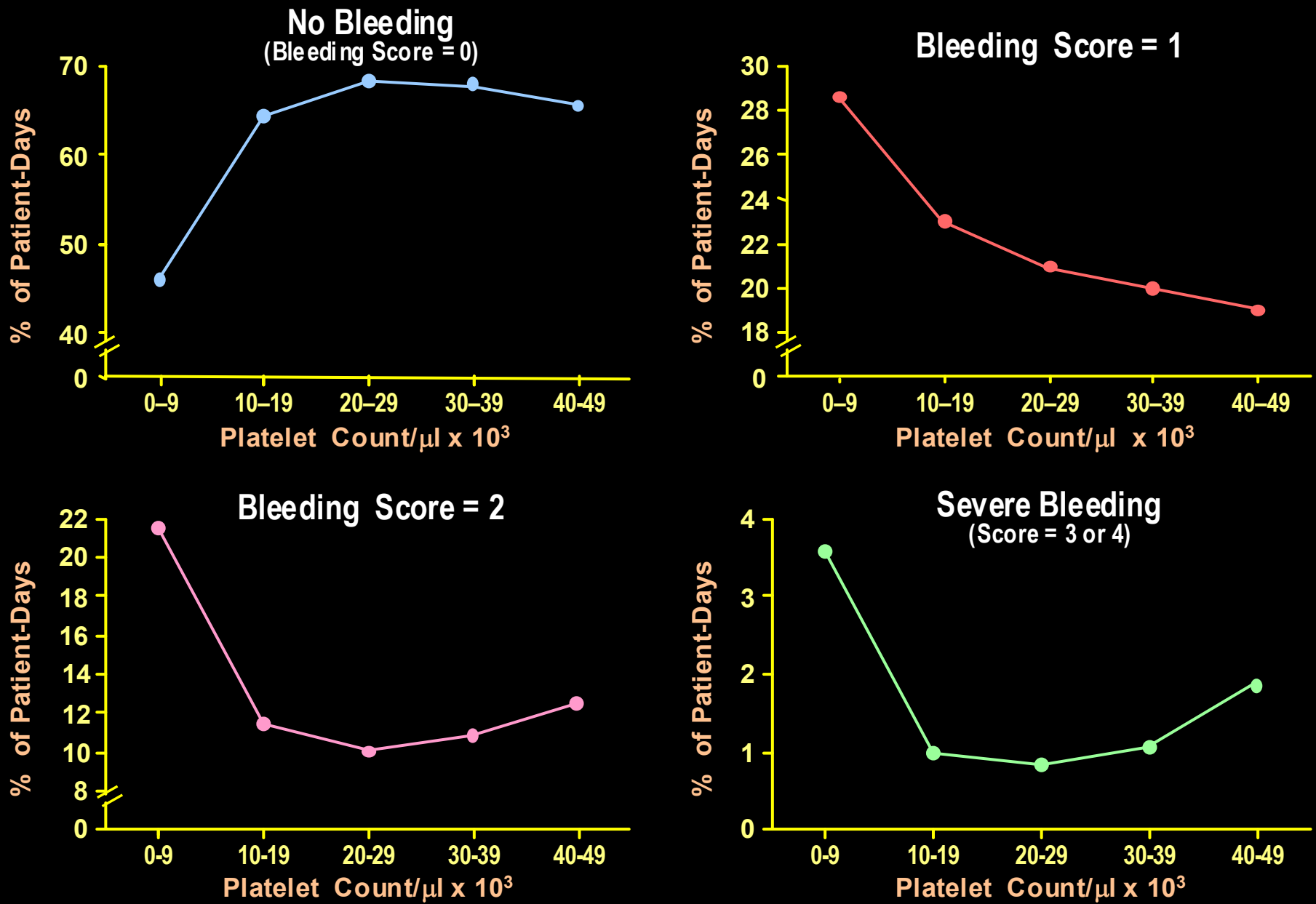


Relationship between bleeding and first morning platelet count shown as the percentage of patient days with each level of bleeding. (The scale on the vertical axis changes with each bleeding level.)

Friedman, *et al.*; *Transfus Med Rev* 2002;16:34.

Predictors of major hemorrhage in AML (WHO Gr 3 or 4)

	Odds Ratio	95% CI
Recent Hemorrhage (<6 days)	6.72	5.53 – 8.18
Uremia (BUN >50)	1.64	1.40 – 1.92
Hypoalbuminemia (<2 gr)	1,54	1.33 – 1.79
Recent BMT (<100 days)	1.32	1.22 – 1.43

Friedman et al. Transfus Med Rev 2002; 16:34

CONCLUSIONS

- Neither the morning platelet count nor the lowest platelet count of the day have any relationship to risk of major bleeding.
- Bleeding is largely determined by endothelial integrity, local mucosal lesions, or anatomic defects.

Friedman, *et al*.; *Transfus Med Rev* 2002;16:34.

"DETERMINATION OF THE OPTIMAL PROPHYLACTIC PLATELET DOSE STRATEGY TO PREVENT BLEEDING IN THROMBOCYTOPENIC PATIENTS"

(PLADO Trial)

Study was conducted by the
Transfusion Medicine/Hemostasis Clinical Trials Network
supported by the National Heart, Lung, and Blood Institute
of the National Institutes of Health

STUDY DESIGN

Three-Arm Study	Platelets / m^2*
• Lower Dose	1.1×10^{11}
• Medium Dose	2.2×10^{11}
• Higher Dose	4.4×10^{11}

*An acceptable dose was within 25% either above or below the target dose.

PRIMARY ENDPOINT

To compare the three study arms of medium, lower, and higher dose platelet therapy with respect to the percentage of patients experiencing at least one episode of Grade 2 or higher bleeding.

SECONDARY ENDPOINTS

- Highest grade of bleeding during time on study.
- Frequency of bleeding, based on percent of thrombocytopenic days with Grade 2 or higher bleeding.

STUDY POPULATION

MAJOR INCLUSION CRITERIUM

- Patients with hypoproliferative thrombocytopenia who are expected to have a platelet count of ≤10,000/μl for ≥5 days and be in the hospital for ≥5 days.

MAJOR EXCLUSION CRITERIA

- Evidence of ≥ WHO Grade 2 bleeding while being assessed for study entry.
- Patients who will be transfused at a platelet trigger of >10,000 platelets/μl.
- Pre-enrollment lymphocytotoxic antibody screen (PRA) ≥20%.

ACCRUAL REQUIREMENTS

- Total of 1,350 patients - 450 in each of three arms.

RECRUITMENT

- Twenty-six trial sites affiliated with 16 TMH Network centers participated in the study.

STUDY DURATION

- For 30 days from their first platelet transfusion.
- Until they have not received a platelet transfusion for 10 days.
- Until hospital discharge.

HEMOSTATIC ENDPOINTS

	Lower Dose	Medium Dose	Higher Dose	Total
Number of patients enrolled	453	449	449	1351
Primary Endpoint:				
At least one episode of ≥ Grade 2 Bleeding (% of patients)	68%	68%	69%	68%
Secondary Endpoint:				
• Highest grade of bleeding on study (% of patients):				
– None or Grade 1	33%	34%	32%	33%
– Grade 2	56%	58%	59%	58%
– Grade 3	8%	6%	8%	7%
– Grade 4	3%	2%	2%	2%
• Hemorrhagic mortality (# of patients)	0	0	1	1

No significant differences among the arms for any of these endpoints.

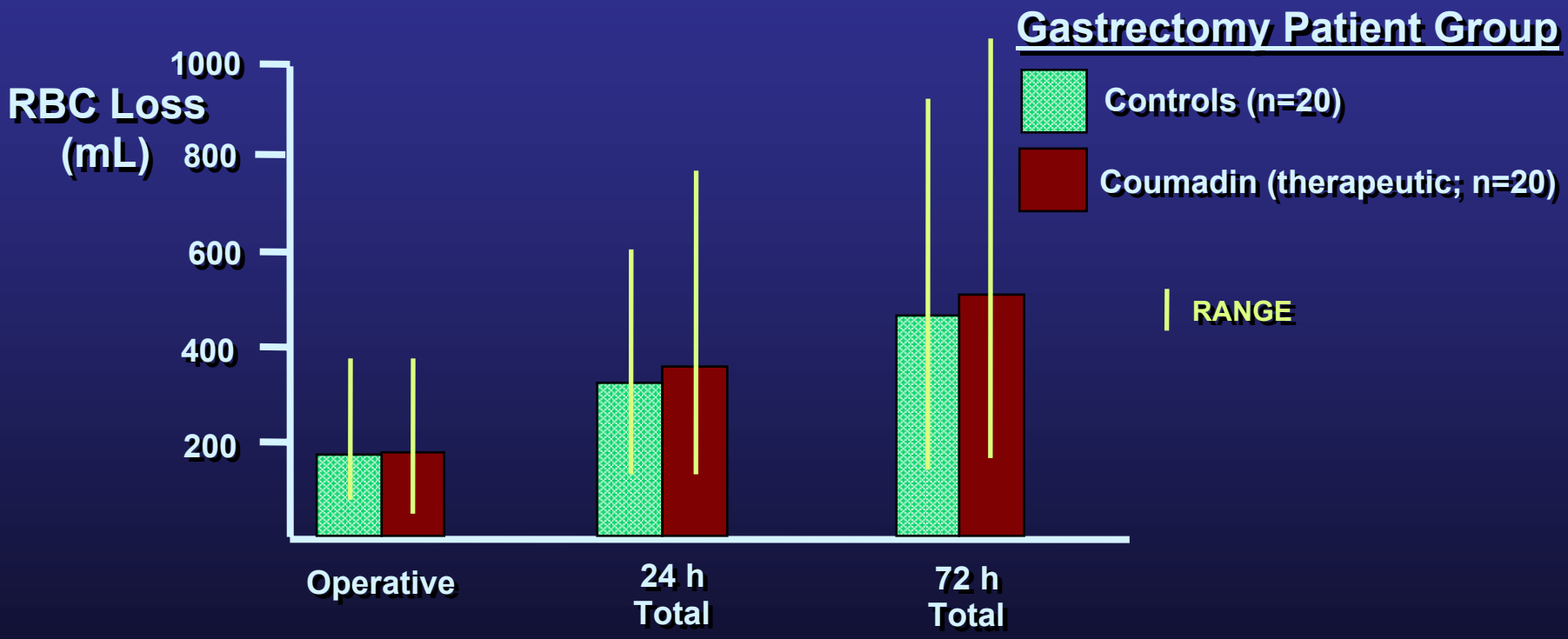
CONCLUSIONS

- The percentage of thrombocytopenic patients with bleeding was not affected by various platelet dose strategies (1.1 - 4.4 x $10^{11}/m^2$ per transfusion).
- The occurrence of $\geq$ Grade 2 bleeding in thrombocytopenic patients remains high -– 68% of patients regardless of the platelet dose.

What do we know about the prophylactic use of plasma?

- That the PT and PTT have never been calibrated to predict bleeding risk. but everyone uses them that way.
- That 40% of plasma used in may large hospitals is used to correct the PT and PTT before low-risk diagnostic procedures.

Effect of Coumadin Treatment on Surgical Blood Loss



Rustad H *et al.* *Acta Med Scand* 1968;178:115-9.

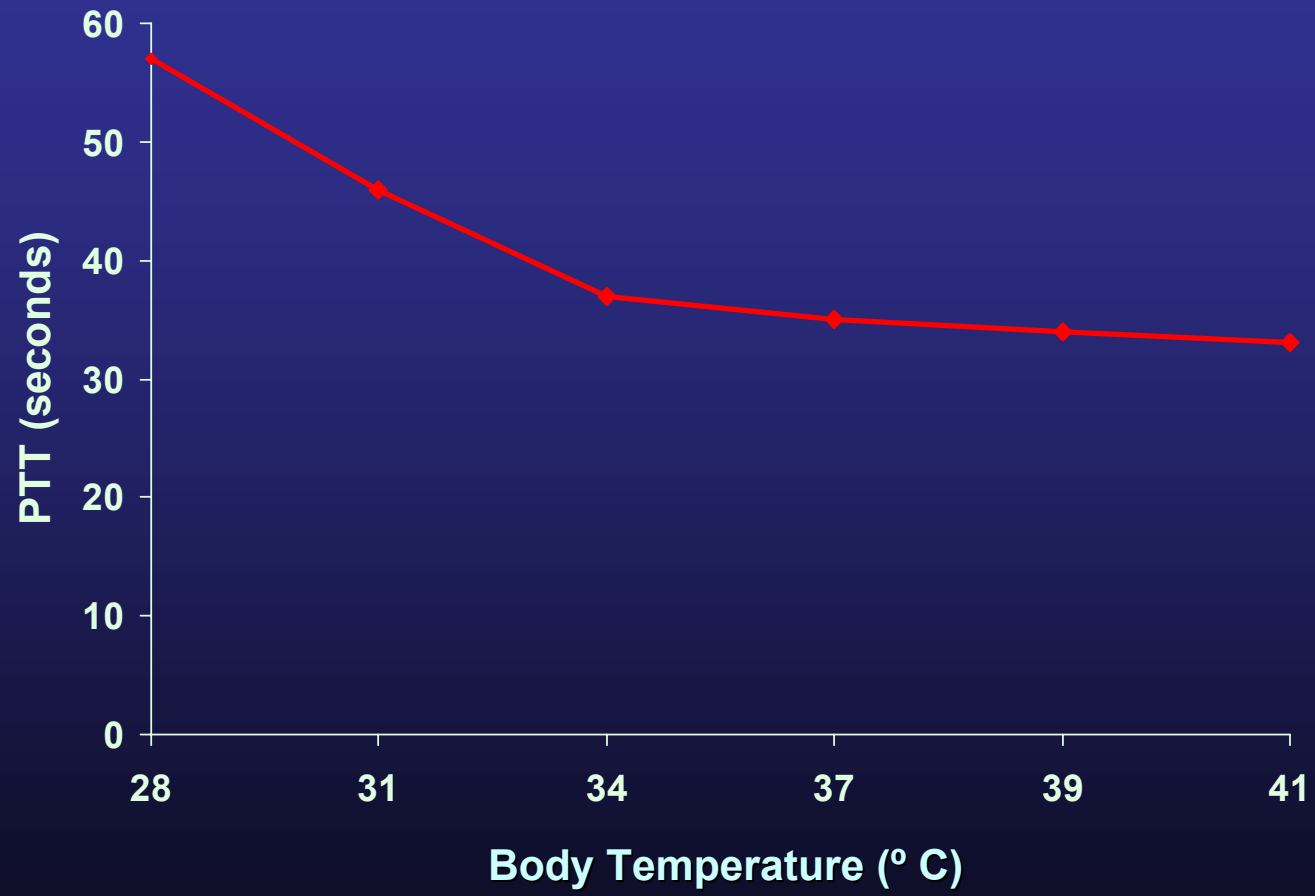
Effect of Coumadin Treatment on Post-Op Blood Loss

Group	n	Post-Op Blood Loss (mL)
Controls	26	813 (125-2125)
Coumadin (therapeutic)	26	624 (210-1650)

Procedure: Mitral commissurotomy

Storm O *et al.* *Circ* 1955;12:961-5.

Effect of Body Temperature on Coagulation



Rohrer MJ, Natale AM. *Crit Care Med* 1992;20:1402-5.

TABLE 29—MANAGING PATIENTS WITH HIGH INR VALUES

CLINICAL SITUATION	GUIDELINES
INR > therapeutic range but < 5.0; no significant bleeding	Lower the dose; or omit the next dose, and resume therapy at a lower dose when the INR is within therapeutic range; if the INR is only slightly above therapeutic range, dose reduction may not be necessary (**grade 2C**)
INR > 5.0 but < 9.0; no significant bleeding	Omit the next dose or two, monitor INR more frequently, and resume therapy at a lower dose when the INR is within therapeutic range Alternatively, omit a dose and give vitamin K[1] (1 to 2.5 mg orally), especially if the patient is at increased risk for bleeding Patients requiring more rapid reversal before urgent surgery: vitamin K_1 (2 to 4 mg orally); if INR remains high at 24 h: an additional dose of vitamin K[1] (1 to 2 mg orally) (all **grade 2C**, compared with no treatment)
INR > 9.0; no significant bleeding	Omit warfarin; give vitamin K_1 (3 to 5 mg orally); closely monitor the INR; if the INR is not substantially reduced in 24 to 48 h, monitor the INR more often, giving additional vitamin K_1, if necessary Resume therapy at a lower dose when the INR is within therapeutic range (both **grade 2C**, compared with no treatment)
INR > 20; serious bleeding	Omit warfarin; give vitamin K_1 (10 mg, slow IV infusion), supplemented with fresh plasma or prothrombin complex concentrate, depending on urgency; vitamin K_1 injections can be repeated every 12 h (**grade 2C**)
Life-threatening bleeding	Omit warfarin; give prothrombin complex concentrate with vitamin K_1 (10 mg by slow IV infusion); repeat if necessary, depending on the INR (**grade 2C**)

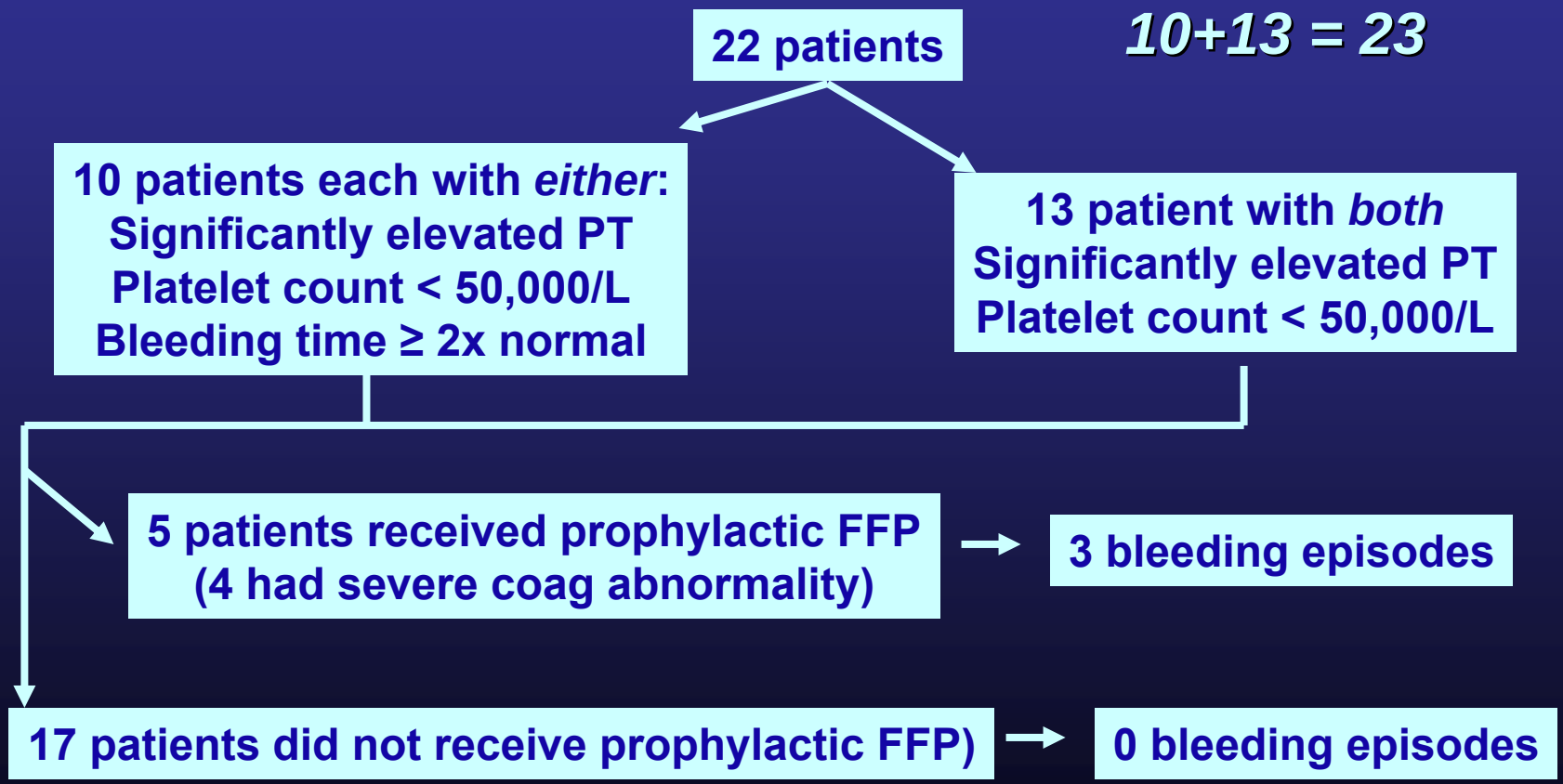
- **Lower dose or omit dose, restart when in range**
- **Vit K 0.5-1.0 IV**
- **Vit K 3-5 q 6-12 h**
- **Vit K 10 mg IV q 12 h**

Hirsh. Chest 1992; 102(suppl):312s-26s

http://www.chestnet.org/guidelines/antithrombotic/p17.php

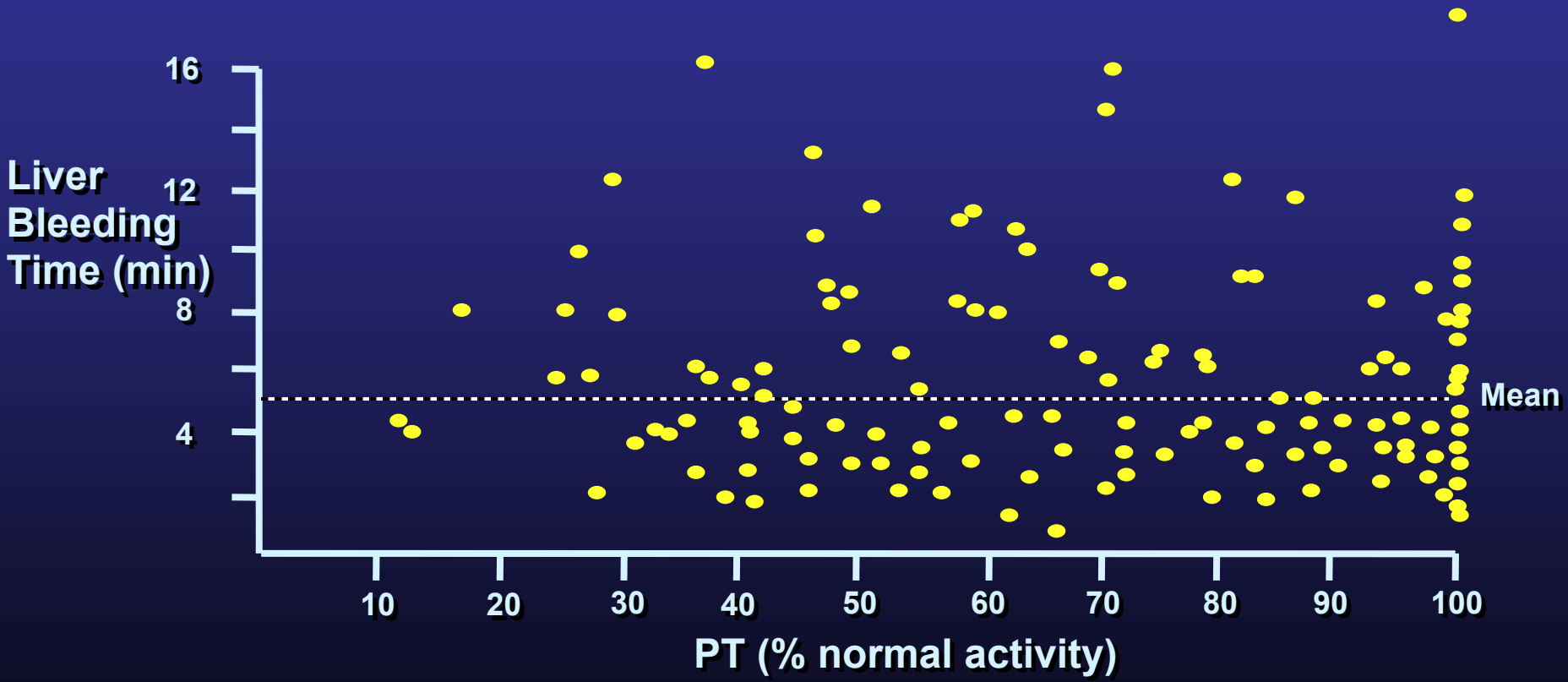
Predicting Hemorrhage After Liver Biopsy

58 *laparoscopic* biopsies – 22 consecutive patients



Inabnet WB, Deziel DJ. *Am Surg* 1995;61:603-6.

Poor Predictive Power of PT Prior to *Laparoscopic* Liver Needle Biopsy



Note: 10% change in activity = approximately 1 sec

Ewe K. Dig Dis Sci 1981;26:388-93.

Studies in Other Invasive Procedures

Paracentesis/thoracentesis

395 patients with mild/moderate PT abnormalities (up to 2x midpoint reference range)

→ No difference in bleeding if did/not get plasma

Transbronchial biopsy

Coagulation tests not predictive

Line placement

Prediction of bleeding by multiple parameters

McVay PA, Toy PT. Transfusion 1991;31:164-71
Bjortuft O et al. Eur Respir J 1998;12:1025-7.
DeLoughery TG et al. Transfusion 1996;36:827-31

Line Placement and Bleeding Risk
according to score and service

HDS Score	Medical	Surgical	Trauma	Total
0	0/37	1/320 (0.3%)	0/42	1/299 (<1%)
1-7	7/77 (9%)	2/194 (1%)	1/84 (1%)	10/355 (<3%)
≥8	4/8 (50%)	0/4	1/11 (9%)	5/23 (22%)
Total	11/22 (9%)	3/518 (0.6%)	2/137 (1.4%)	16/777 (2%)

3 points = PT 18-24, PTT 48-64, Platelets 20-49,000, Creatinine > 1.4
4 points = PT >24, PTT >64, Platelets <20,000

DeLoughery TG *et al.* *Transfusion* 1996;36:827-31

Bleeding During Fine Needle Aspiration Biopsies

Congenital or acquired hemostatic defects (21 patients)

Most common: Coumadin therapy (12)

↓

Fine needle aspiration/biopsy (superficial sites)

Most common: Lymph node (7)

↓

Complications: Small ecchymosis (1 patient)
No FFP required for any patient

Jadusingh IH et al. Acta Cytol 1996;40:472-4

What is the best anticoagulant for cancer-associated thrombosis?

- Aspirin?
  - May cause ulcers, especially in sick people
  - Not immediately reversable
- Heparin?
  - Risk of HIT, HITT, and not reversible, but short lasting
- Low-molecular weight heparin?
  - Not reversible, long lasting
- Coumadin?
  - Cheap, oral, hard to regulate given diet

What is the best anticoagulant for cancer-associated thrombosis?

- Lee AY, et al. Low-molecular weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003; 349:146-53.
  - LMW heparin reduced the rate of recurrent VTE 52% more than coumadin
  - Authors advise to continue therapy for 6 months after first clot.


Thank you
Gracias