SIOP PODC Supportive Care Education
Presentation Date: 24th November 2015
Recording Link at www.cure4kids.org:
https://www.cure4kids.org/ums/home/conference_rooms/enter.php?room=p423n9gn76r

Management of thrombocytopenia during cancer therapy

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CEO, Resonance Oncology
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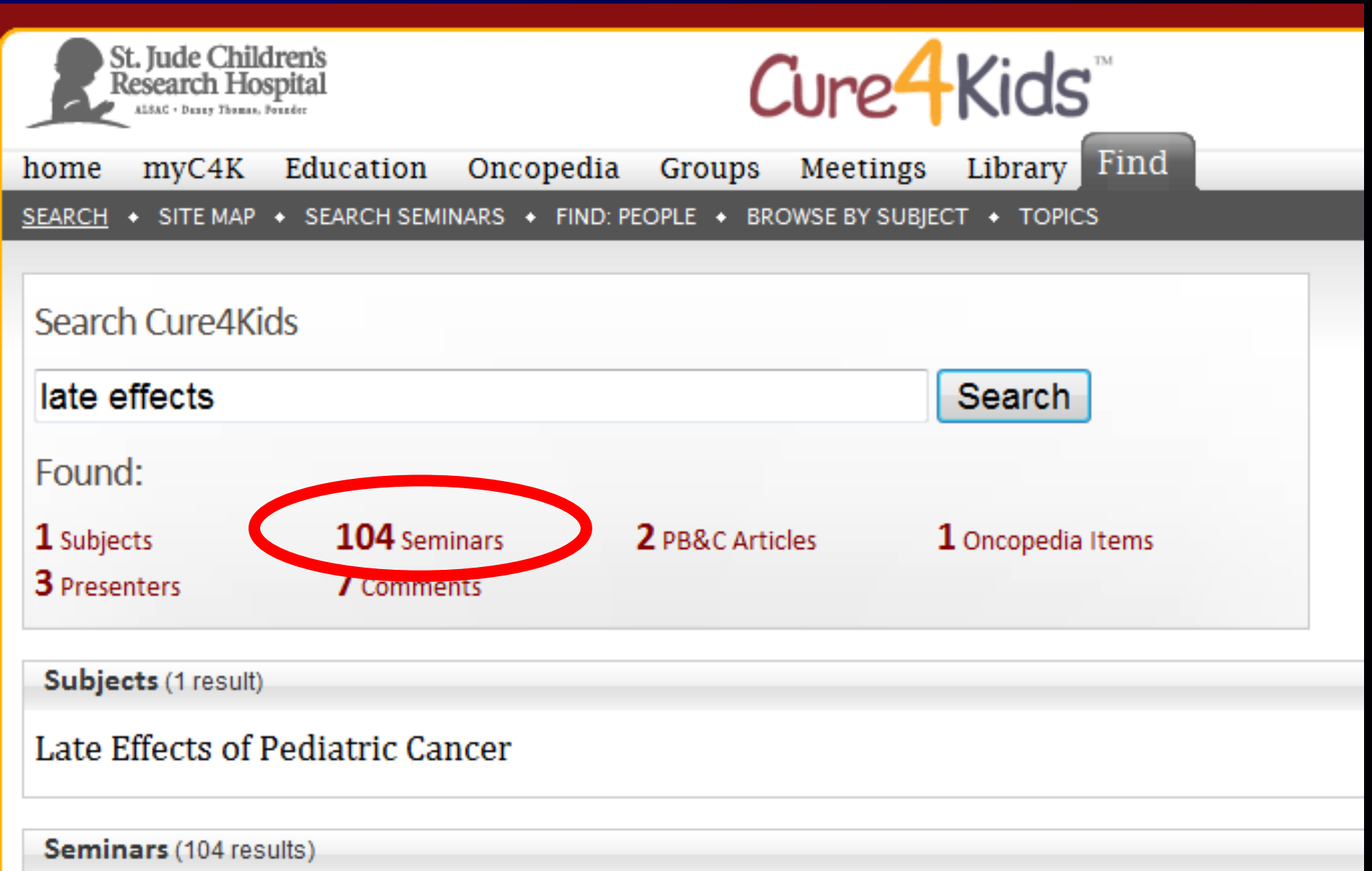
Learning Objectives

- Define major, minor, and trivial hemorrhage
- Review the indications for prophylactic transfusion of platelets in cancer patients
- Identify safe platelet counts for invasive procedures
- Assess the optimal volume of platelets for small children who require transfusion

Cure4Kids Seminars – Late Effects



Major points

- Hemorrhage should be rapidly treated
- Most patients: prophylactic platelet transfusion when the platelets <10,000
- Higher or lower thresholds in special situations – RISK vs. BENEFITS
- No premedication with antihistamines or antipyretics
- One pheresed unit (4-6 buttons) for most patients, 10-20 mL/kg for small children

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

journal homepage: www.tmreviews.com

Original Articles

Guidance on Platelet Transfusion for Patients With Hypoproliferative Thrombocytopenia

See Editorial, pages 1–2

Susan Nahirniak [a,*], Sherrill J. Slichter [b], Susano Tanael [c], Paolo Rebulla [d], Katerina Pavenski [e], Ralph Vassallo [f], Mark Fung [g], Rene Duquesnoy [h], Chee-Loong Saw [i], Simon Stanworth [j], Alan Tinmouth [k], Heather Hume [l], Arjuna Ponnampalam [m], Catherine Moltzan [n], Brian Berry [o], Nadine Shehata [p], for the International Collaboration for Transfusion Medicine Guidelines (ICTMG)

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[i] HLA Laboratory, Hematology Division, McGill University Health Centre, Montreal, Canada
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[k] Department of Medicine, Ottawa Hospital and University of Ottawa, and the Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Canada
[l] Département de Pédiatrie, Universtié de Montréal, CHU Sainte-Justine Montréal, Montreal, Canada
[m] Department of Pathology, University of Manitoba, Winnipeg, Canada
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[o] Division of Medical Sciences, University of Victoria, Victoria, Canada
[p] Departments of Medicine and Obstetric Medicine, Mount Sinai Hospital, Toronto, Canada

Question 1: Should Patients With Hypoproliferative Thrombocytopenia Receive Prophylactic Platelet Transfusions?

Recommendation 1

Prophylactic platelet transfusion should be given to patients with hypoproliferative thrombocytopenia (moderate level of evidence, strong recommendation for adults and weak level of evidence, strong recommendation for pediatric patients).

Question 2: What Platelet Transfusion Threshold Should Be Used?

Recommendation 2

A threshold of less than or equal to 10×10^9/L should be used for prophylactic platelet transfusion for patients with hypoproliferative thrombocytopenia (moderate level of evidence, strong recommendation for adults and weak level of evidence, strong recommendation for pediatric patients).

Recommendation 3

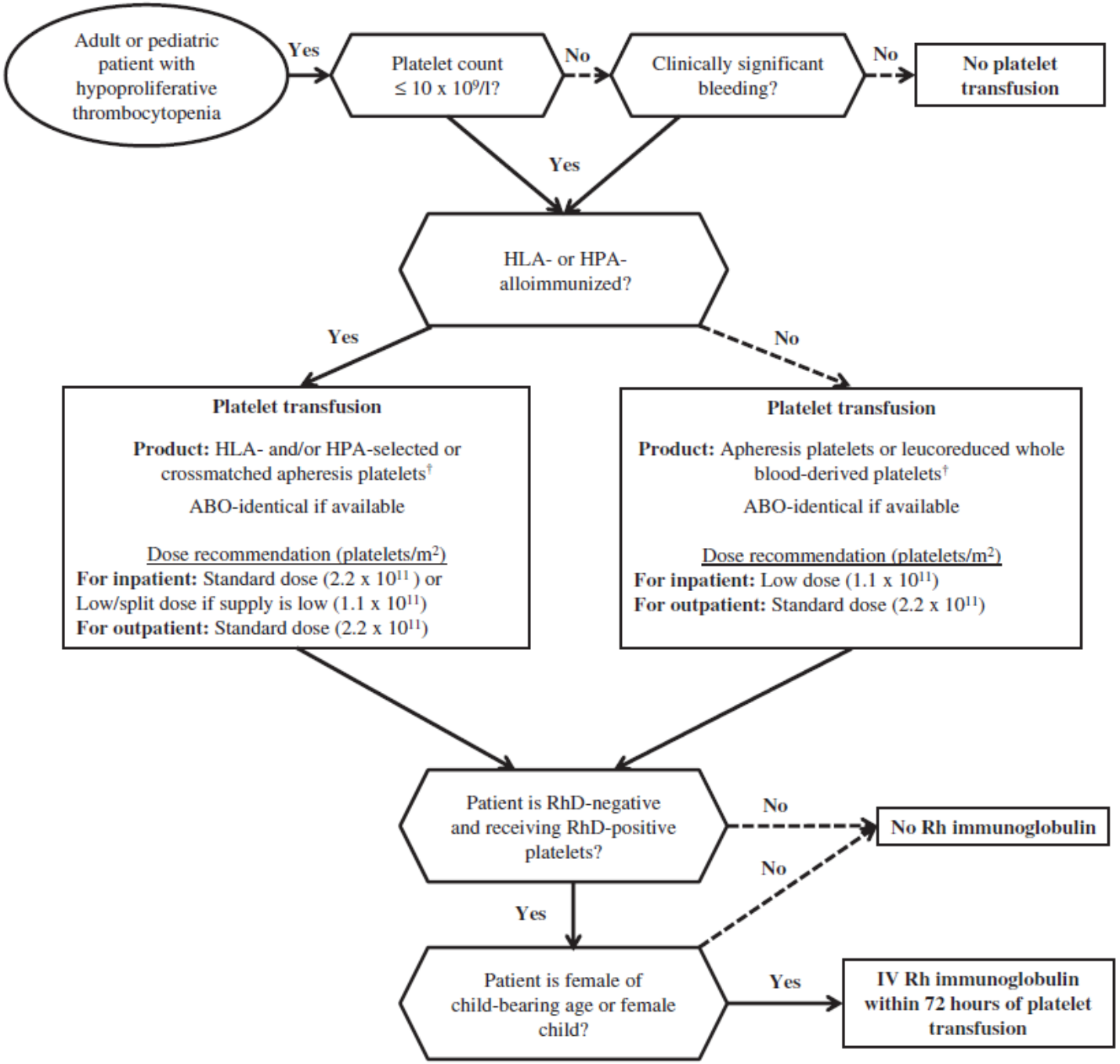
Patients with hypoproliferative thrombocytopenia with clinically significant bleeding attributed to thrombocytopenia should probably receive platelet transfusions even if the platelet count is above 10×10^9/L (very weak level of evidence, weak recommendation).

Question 3: What Platelet Dose Should Be Used?

Recommendation 4

Low- or standard-dose platelet transfusion (ie, $1.1 \times 10^{11}/m^2$ or $2.2 \times 10^{11}/m^2$, respectively), as opposed to high-dose platelet transfusion ($4.4 \times 10^{11}/m^2$), should be given to hospitalized patients with hypoproliferative thrombocytopenia who require prophylactic platelet transfusion (high level of evidence, strong recommendation).

(Conversion to platelet units can be performed using estimates of 50×10^9 per unit of WBD random-donor platelet products or 300×10^9 per unit apheresis or buffy coat pooled products.)


Adult or pediatric patient with hypoproliferative thrombocytopenia
Yes
Platelet count ≤ 10 x 10⁹/l?
No
Clinically significant bleeding?
No
No platelet transfusion
Yes
HLA- or HPA-alloimmunized?
Yes
No
Platelet transfusion
Product: HLA- and/or HPA-selected or crossmatched apheresis platelets†
ABO-identical if available
Dose recommendation (platelets/m²)
For inpatient: Standard dose (2.2 x 10¹¹) or Low/split dose if supply is low (1.1 x 10¹¹)
For outpatient: Standard dose (2.2 x 10¹¹)
Platelet transfusion
Product: Apheresis platelets or leucoreduced whole blood-derived platelets†
ABO-identical if available
Dose recommendation (platelets/m²)
For inpatient: Low dose (1.1 x 10¹¹)
For outpatient: Standard dose (2.2 x 10¹¹)
Patient is RhD-negative and receiving RhD-positive platelets?
No
No Rh immunoglobulin
No
Yes
Patient is female of child-bearing age or female child?
Yes
IV Rh immunoglobulin within 72 hours of platelet transfusion

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
Vox Sanguinis (2012) **103**, 284–293

ORIGINAL PAPER

DOI: 10.1111/j.1423-0410.2012.01627.x

Platelet transfusions in haematology patients: are we using them appropriately?

L. J. Estcourt,[1] J. Birchall,[2] D. Lowe,[3] J. Grant-Casey,[4] M. Rowley[5] & M. F. Murphy[1]

[1] *NHS Blood and Transplant, and the NIHR Biomedical Research Centre, John Radcliffe Hospital, Oxford, UK*
[2] *NHS Blood and Transplant, Bristol and North Bristol NHS Trust, Bristol, UK*
[3] *Royal College of Physicians, London, UK*
[4] *NHS Blood and Transplant, Oxford, UK*
[5] *NHS Blood and Transplant, London and Imperial NHS Trust, London, UK*

Vox Sanguinis

Background and Objectives A large proportion of all platelet components are given to haematology patients. As there are risks associated with their transfusion, costs associated with production, and shortages may occur, it is important that their use is appropriate.

Study Design and Methods The study was split into two parts, a survey to assess local practice guidelines and an assessment of platelet usage. A total of 123 hospitals completed the survey and 168 hospitals submitted data of 40 haematology patients over a 3-month period.

Results The organizational survey found that 36% of hospitals routinely give prophylactic platelet transfusions to patients with long-term bone-marrow failure. Also, a significant minority of hospitals administer platelet transfusions if the platelet count is below a certain threshold prior to performing a bone-marrow aspirate (11%) or a bone-marrow aspirate and trephine (23%); both of these are contrary to UK platelet transfusion guidelines. Data were collected on a total of 3402 patients, of which 3296 cases were eligible for analysis. They received approximately 46% of all platelet components issued to participating hospitals in England during the study period. The majority (69%) of platelet transfusions were prophylactic; of these only 33% were given when the platelet count was $\leq 10 \times 10^9$/l. Using an algorithm,

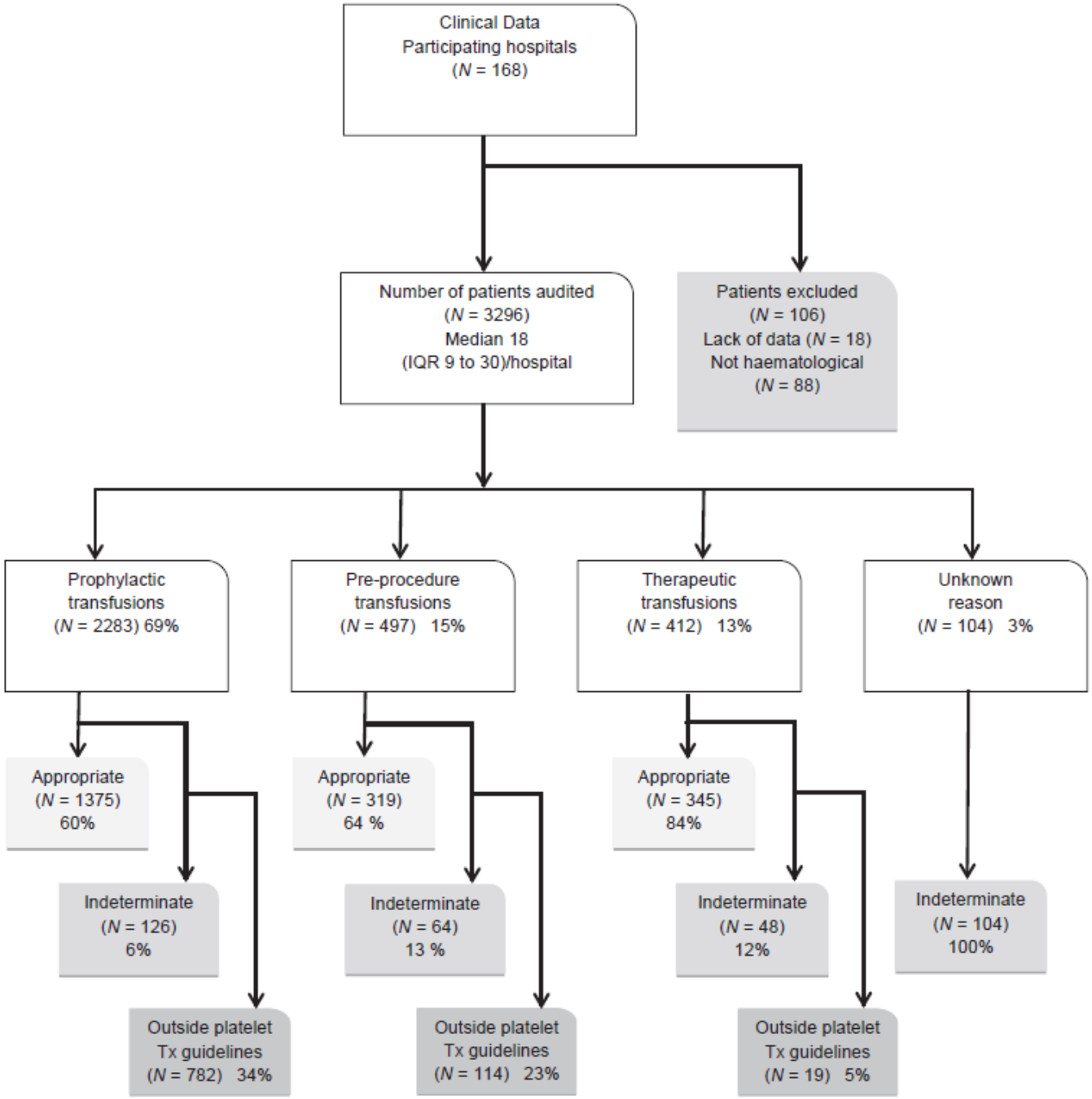


Fig. 1 Flow diagram of cases included in study.

Learning Objectives

- **Define major, minor, and trivial hemorrhage**
- **Review the indications for prophylactic transfusion of platelets in cancer patients**
- **Identify safe platelet counts for invasive procedures**
- **Assess the optimal volume of platelets for small children who require transfusion**

Bleeding

From Wikipedia (View original Wikipedia Article) Last modified on 30 September 2010 at 17:16

(Redirected from WHO bleeding scale)

For other uses, see Bleeding (disambiguation).

"Hemorrhage" redirects here. For the song by Fuel, see Hemorrhage (In My Hands).

"Haemorrhage" redirects here. For the band, see Haemorrhage (band).

For the deliberate extraction of blood, see Bloodletting.

This article **needs additional citations for verification.**
Please help by adding reliable references. Unsourced material may be challenged and removed. *(August 2007)*

Bleeding, technically known as **hemorrhaging** or **haemorrhaging** (see American and British spelling differences) is the loss of blood or blood escape from the circulatory system.[1] Bleeding can occur internally, where blood leaks from blood vessels inside the body or externally, either through a natural opening such as the vagina, mouth, nose, ear or anus, or through a break in the skin. The complete loss of blood is referred to as exsanguination,[2] and desanguination is a massive blood loss. Typically, a healthy person can endure a loss of 10-15% of the total blood volume without serious medical difficulties, and blood donation typically takes 8-10% of the donor's blood volume.[3]

Bleeding

Classification and external resources

A bleeding human finger

ICD-10	R 58.
MeSH	D006470

New Strategies for the Optimal Use of Platelet Transfusions

Morris A. Blajchman,[1] Sherrill J. Slichter,[2] Nancy M. Heddle,[3] and Michael F. Murphy[4]

Table 1. Summary of the main features of the use of platelet transfusions in three multicenter RCTs that have either recently been completed (PLADO), stopped (SToP), or is ongoing (TOPPS) evaluating different strategies for use in thrombocytopenic patients with a hypoproliferative marrow.

	PLADO	SToP	TOPPS
Type of platelet transfusion intervention	Prophylactic	Prophylactic	Therapeutic vs prophylactic
Primary Endpoint	WHO Bleeding (grade 2 or greater)	WHO Bleeding (grade 2 or greater)	WHO Bleeding (grade 2 or greater)
Projected sample size, n	1350 (3 arms)	270 (2 arms)	300 (2 arms)
Arm 1 intervention	1.1×10^{11} platelets/m^2	1.5 to 2.9×10^{11} platelets	Prophylactic platelet transfusions with a trigger of 10×10^9/L
Arm 2 intervention	2.2×10^{11} platelets/m^2	3.0 to 6.0×10^{11} platelets	Therapeutic platelet transfusions only
Arm 3 intervention	4.4×10^{11} platelets/m^2	N/A	N/A
Study Status	Concluded; data being analyzed	Stopped by DSMB (n = 130)	Ongoing

Abbreviations: PLADO, Prophylactic PLAtelet Dose study; SToP, Strategies for the Transfusion of Platelets study; TOPPS, Trial Of Prophylactic Platelets Study; N/A, not applicable; DSMB, data safety monitoring board; WHO, World Health Organization.

WHO bleeding scale

WHO bleeding scale

The World Health Organization, or WHO, made a standardized grading scale to measure the severity of bleeding.

Grade 0	no bleeding
Grade 1	petechial bleeding;
Grade 2	mild blood loss (clinically significant);
Grade 3	gross blood loss, requires transfusion (severe);
Grade 4	debilitating blood loss, retinal or cerebral associated with fatality

References

- Webert KE, Cook RJ, Sigouin CS, et al. The risk of bleeding in thrombocytopenic patients with acute myeloid leukemia. haematologica 2006;91:1530-1537

http://www.worldlingo.com/ma/enwiki/en/WHO_bleeding_scale

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.02

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the colon.					
Colonic fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the large intestine and another organ or anatomic site.					
Colonic hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the colon.					

Define Types of Hemorrhage

- **Major**
  - **Fatal (CTCAE grade 5, WHO grade 4)**
  - **Life-threatening (CTCAE grade 4, WHO 4)**
  - **Requiring transfusion or other urgent intervention (CTCAE grade 3, WHO grade 3)**
- **Minor – clinically significant but not urgent (CTCAE grade 2, WHO grade 2)**
- **Trivial – petechiae, transient nose-bleed, microscopic hematuria, scleral hemorrhage**

Learning Objectives

- Define major, minor, and trivial hemorrhage
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Clinical Practice

- How many people use a prophylactic platelet transfusion threshold of:
  - 0
  - 5,000
  - 10,000
  - 15,000
  - 20,000
  - >20,000

A Question

- **How many platelets should one transfuse for life-threatening thrombocytopenic bleeding?**

A Question

- **How many platelets should one transfuse for life-threatening thrombocytopenic bleeding?**

  A. 1 button

  B. 1 pheresed unit

  C. Many pheresed units

  D. Depends on the child's weight

A Question

- How many platelets should one transfuse for life-threatening thrombocytopenic bleeding?
  - A. 1 button
  - B. 1 pheresed unit (appetizer)
  - C. Many pheresed units (entrée)
  - D. Depends on the child's weight

The Effect of Thrombocytopenia on BT

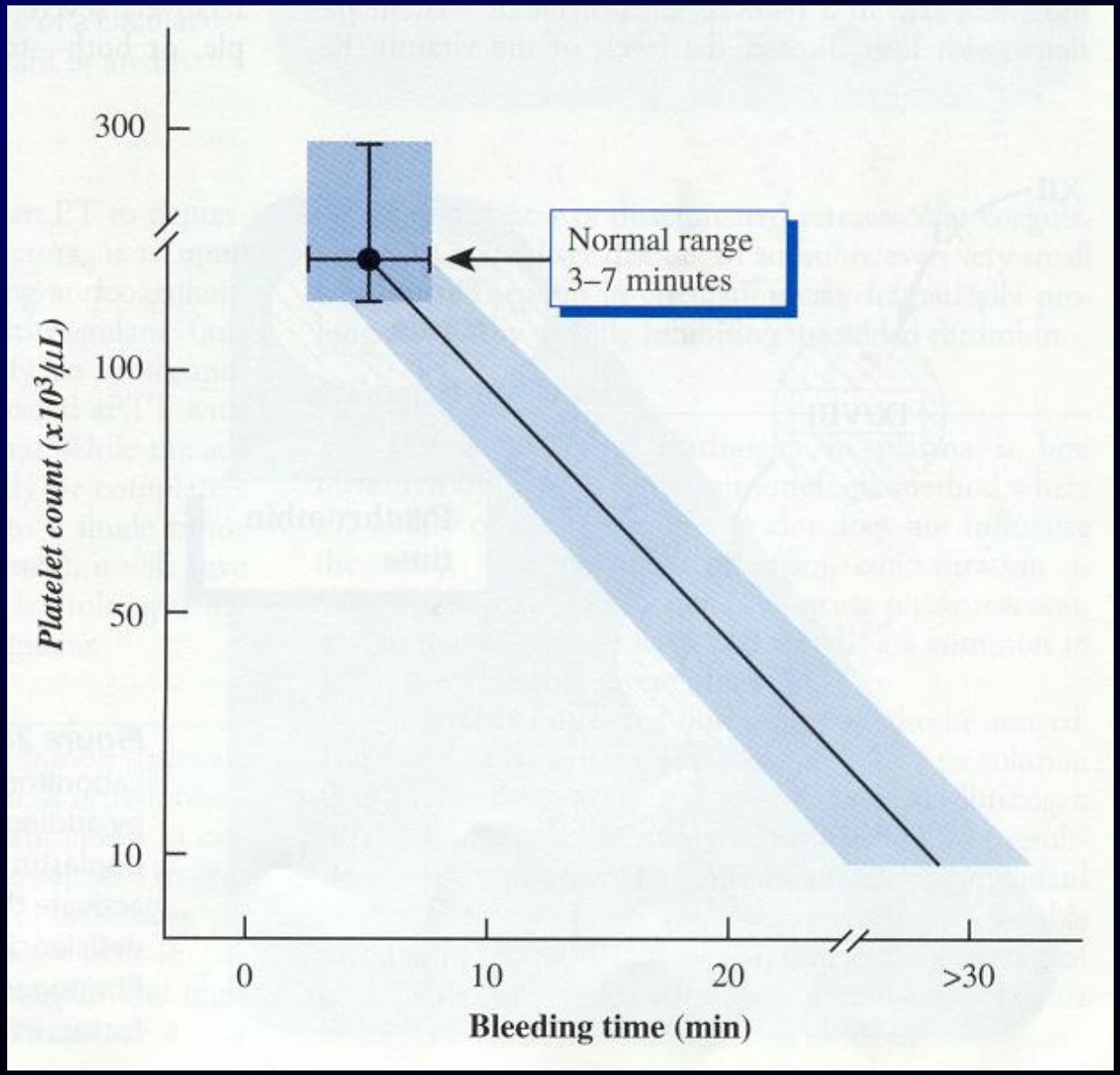
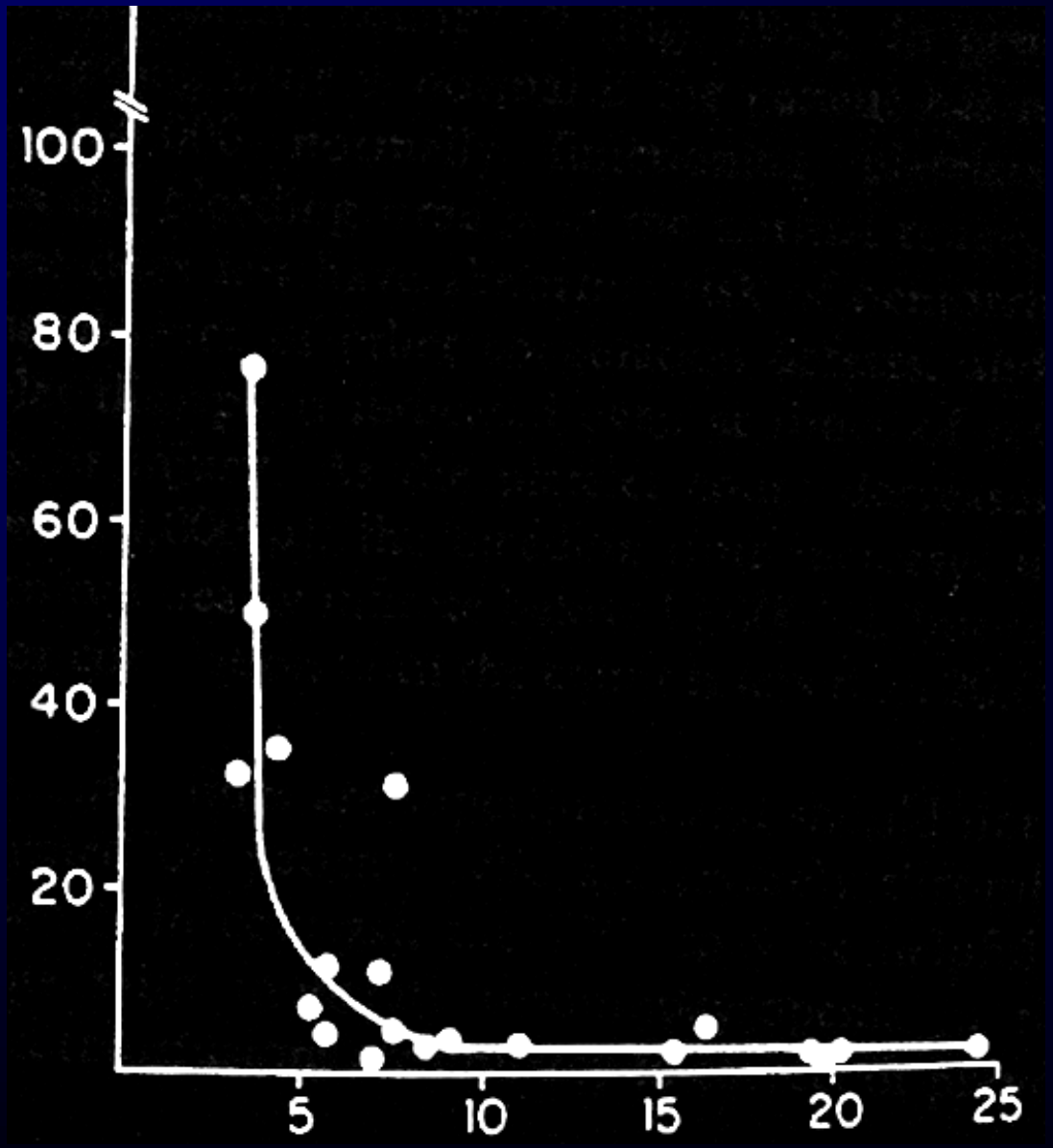


Figure 28-1

Stool Blood Loss in Aplastic Anemia



Platelet Transfusion - Prophylaxis

- NIH Consensus conference (1986): Threshold of 20,000 can sometimes be safely lowered.
- Royal College of Physicians, Edinburgh (1997) Threshold of 10,000 in absence of additional risk factors.
- Some authors (Slichter 1991, Beutler 1993): Threshold of 5,000 in stable patients.
- Others: threshold of 0,000 (therapeutic transfusion only, with no prophylactic transfusion) in the closely monitored setting (Murphy, Am J Hematol 12: 347-56, 1982; Solomon et al, Lancet 1: 267, 1978).

Platelet Transfusion - Prophylaxis

- 102 patients with ANLL
- Sliding scale based on AM platelet count:
  - 0-5K: Platelets transfused
  - 6-10K: Fever (>38C) or minor hemorrhage
  - 11-20K: Heparin/Coag disorders, before minor procedures
  - >20K: Significant bleeding
- Results
  - Minor hemorrhage common
  - Major hemorrhage on 1.9% of study days
  - Lethal bleeds (n=3): 2 with platelet count >50,000 and DIC, 1 with plt≈1,000 and refractoriness.

Gmur, et.al. Lancet 1991; 338: 1223-6

Gmur et al. Lancet 1991; 338:1223-6

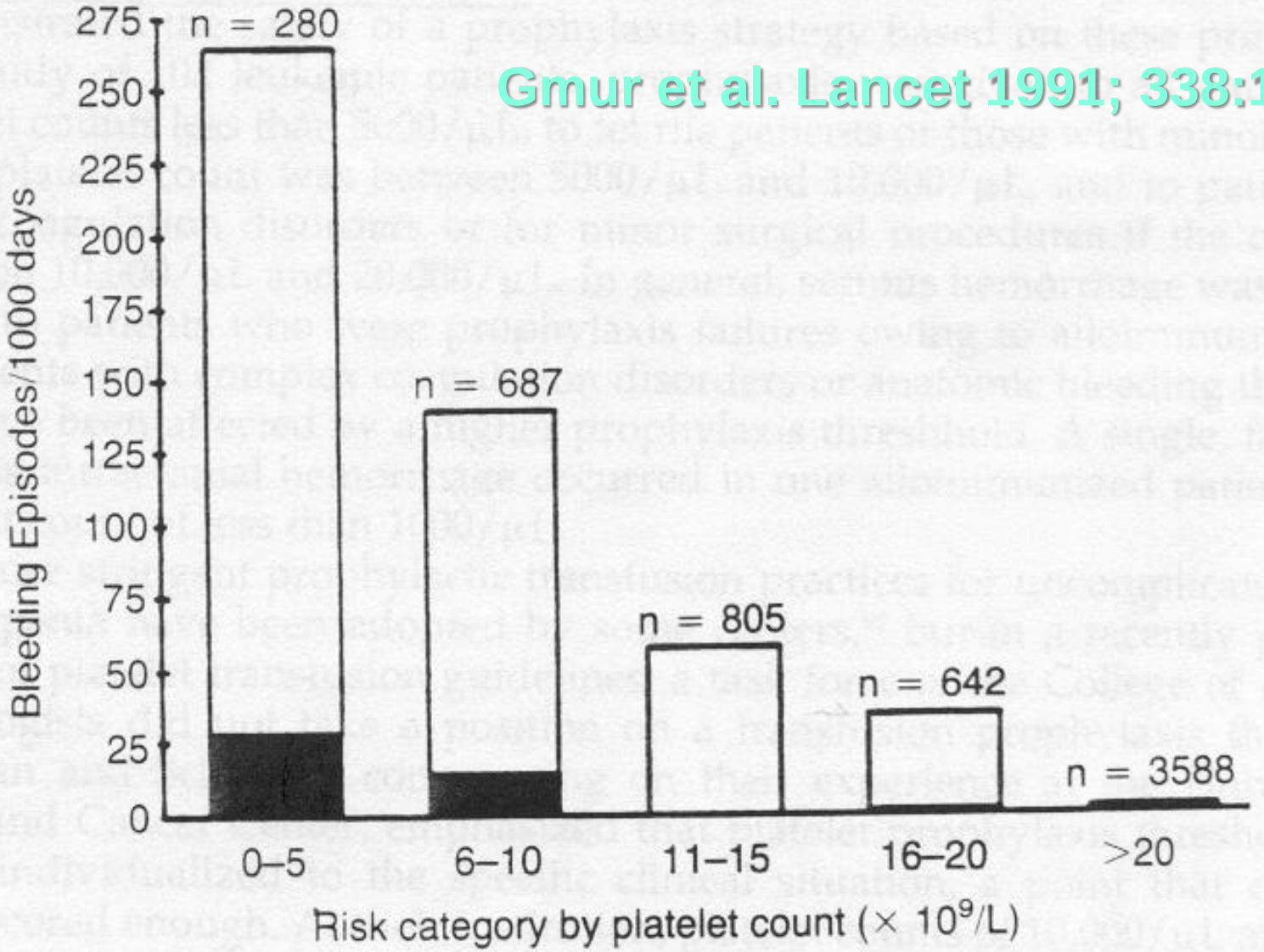


Figure 2. Relationship of bleeding risk to platelet counts in 102 leukemia patients given prophylactic platelet support as described by Gmur. Open bars represent minor bleeding episodes and include mucocutaneous hemorrhage, hematomas not requiring transfusion and retinal hemorrhage not impairing vision. Closed bars represent major bleeding episodes

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Prophylactic Platelet Dose Study (PLADO)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dose of Prophylactic Platelet Transfusions and Prevention of Hemorrhage

Sherrill J. Slichter, M.D., Richard M. Kaufman, M.D., Susan F. Assmann, Ph.D., Jeffrey McCullough, M.D., Darrell J. Triulzi, M.D., Ronald G. Strauss, M.D., Terry B. Gernsheimer, M.D., Paul M. Ness, M.D., Mark E. Brecher, M.D., Cassandra D. Josephson, M.D., Barbara A. Konkle, M.D., Robert D. Woodson, M.D., Thomas L. Ortel, M.D., Ph.D., Christopher D. Hillyer, M.D., Donna L. Skerrett, M.D., Keith R. McCrae, M.D., Steven R. Sloan, M.D., Ph.D., Lynne Uhl, M.D., James N. George, M.D., Victor M. Aquino, M.D., Catherine S. Manno, M.D., Janice G. McFarland, M.D., John R. Hess, M.D., Cindy Leissinger, M.D., and Suzanne Granger, M.S.

Slichter et al. NEJM 2010; 362:600-613

Table 1. Baseline Characteristics of the Study Patients, According to Treatment Group.

Characteristic	Platelet Dose*					
	Low Dose (N=417)	P Value, Low vs. Medium Dose	Medium Dose (N=423)	P Value, Medium vs. High Dose	High Dose (N=432)	P Value, High vs. Low Dose
Age — yr		0.18		0.20		0.02
Median	47		50		51	
Interquartile range	30–57		34–58		32–62	
Sex — no. (%)		0.44		0.83		0.33
Male	243 (58)		258 (61)		267 (62)	
Female	174 (42)		165 (39)		165 (38)	
Weight — kg		0.34		0.82		0.43
Median	80		78		78	
Interquartile range	65–92		60–92		63–91	
Height — cm		0.31		0.22		0.85
Median	170		170		170	
Interquartile range	162–178		160–177		161–178	
Body-surface area — m^2		0.36		0.74		0.54
Median	1.9		1.9		1.9	
Interquartile range	1.7–2.1		1.6–2.1		1.7–2.1	
Previous pregnancy						
No./total no. of women (%)	111/174 (64)	0.09	120/163 (74)	0.11	110/164 (67)	0.69
No. of pregnancies		0.33		0.97		0.32
Median	3		2		3	
Interquartile range	2–4		2–4		2–3	
Previous transfusion — no. (%)						
Platelets	244 (59)	0.67	240 (57)	0.68	240 (56)	0.40
Red cells	316 (76)	0.62	326 (77)	0.13	314 (73)	0.32

Prophylactic Platelet Dose Study (PLADO)

	Low Dose (N=417)	P Value, Low vs. Medium Dose	Medium Dose (N=423)	P Value, Medium vs. High Dose	High Dose (N=432)
Response to prophylactic platelet transfusions					
No. of transfusions	2547		1912		1572
Days until next transfusion¶		<0.001		<0.001	
Median	1.1		1.9		2.9
Interquartile range	0.7–2.1		0.9–3.1		1.2–4.7
No. of transfusions with all data available to calculate 4-hr CCI‖	2193		1646		1386
Pretransfusion platelet count — $\times 10^{-3}/mm^3$		0.48		0.08	
Median	9		9		9
Interquartile range	7–16		7–19		7–12
Post-transfusion platelet count — $\times 10^{-3}/mm^3$**		<0.001		<0.001	
Median	22		34		50
Interquartile range	16–30		24–48		33–68

- The trigger threshold of 10,000 platelets/mm^3 was adhered to on 90%, 92%, and 94% of patient-days in the low-dose group, medium-dose group, and high-dose group, respectively

Slichter et al. NEJM 2010; 362:600-613

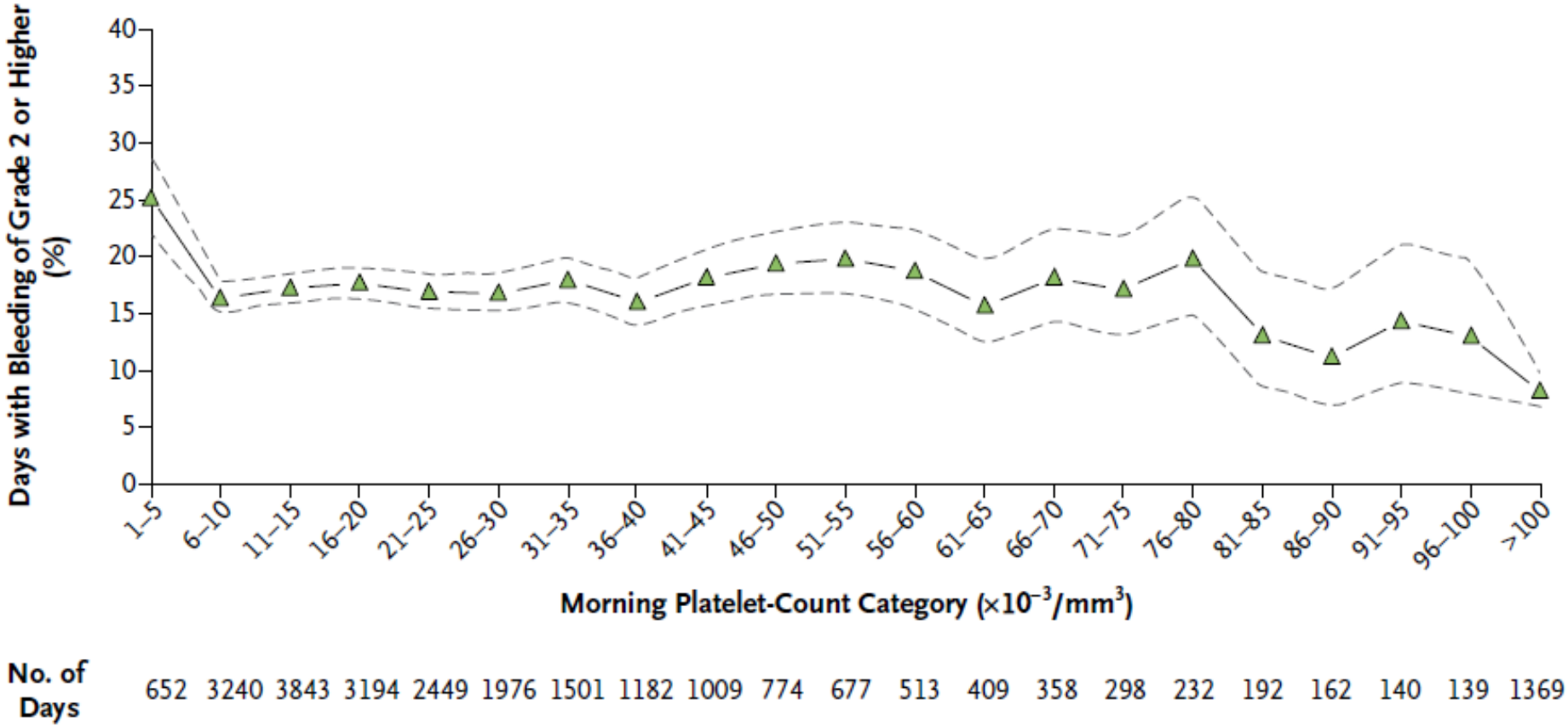
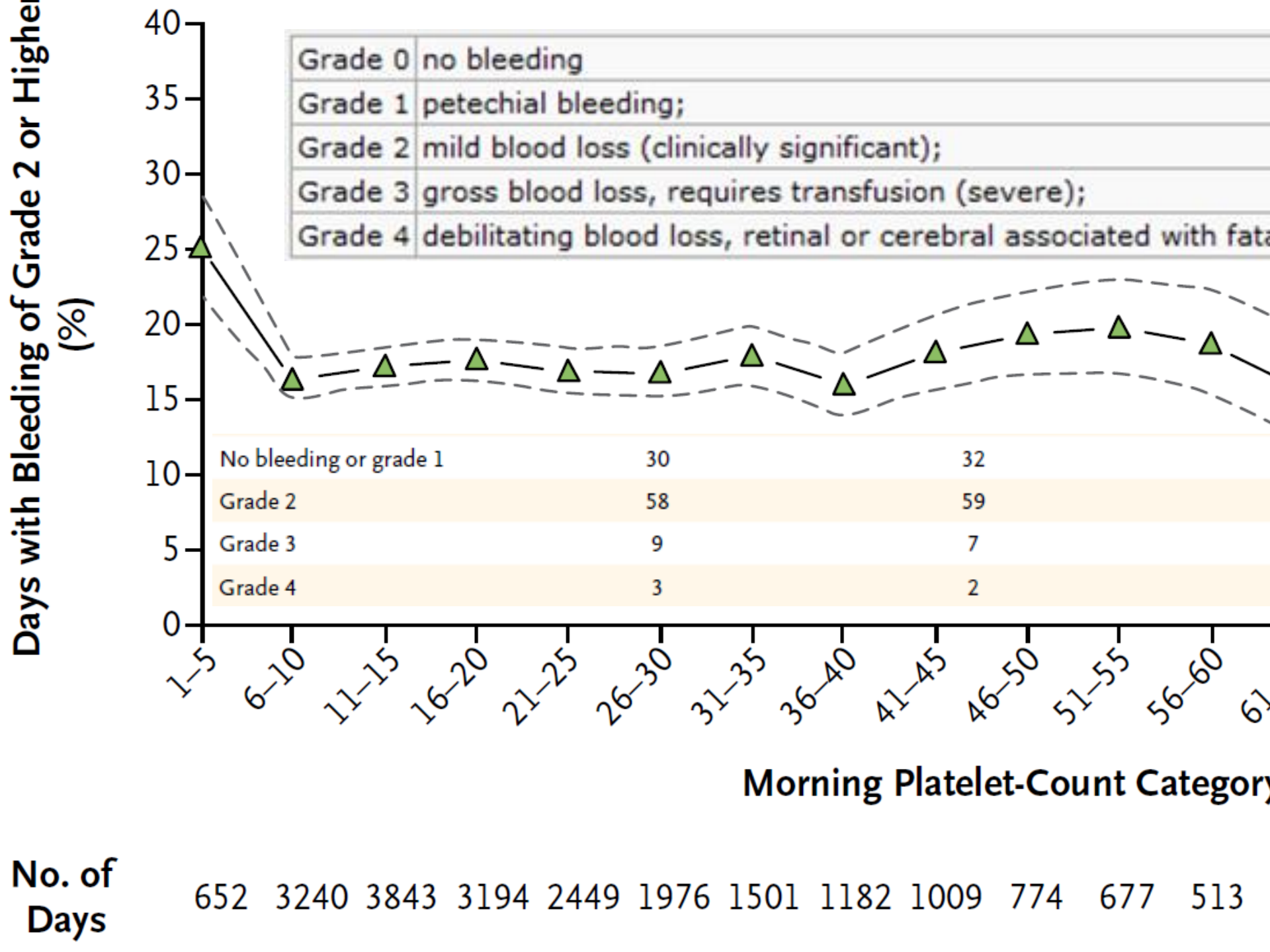
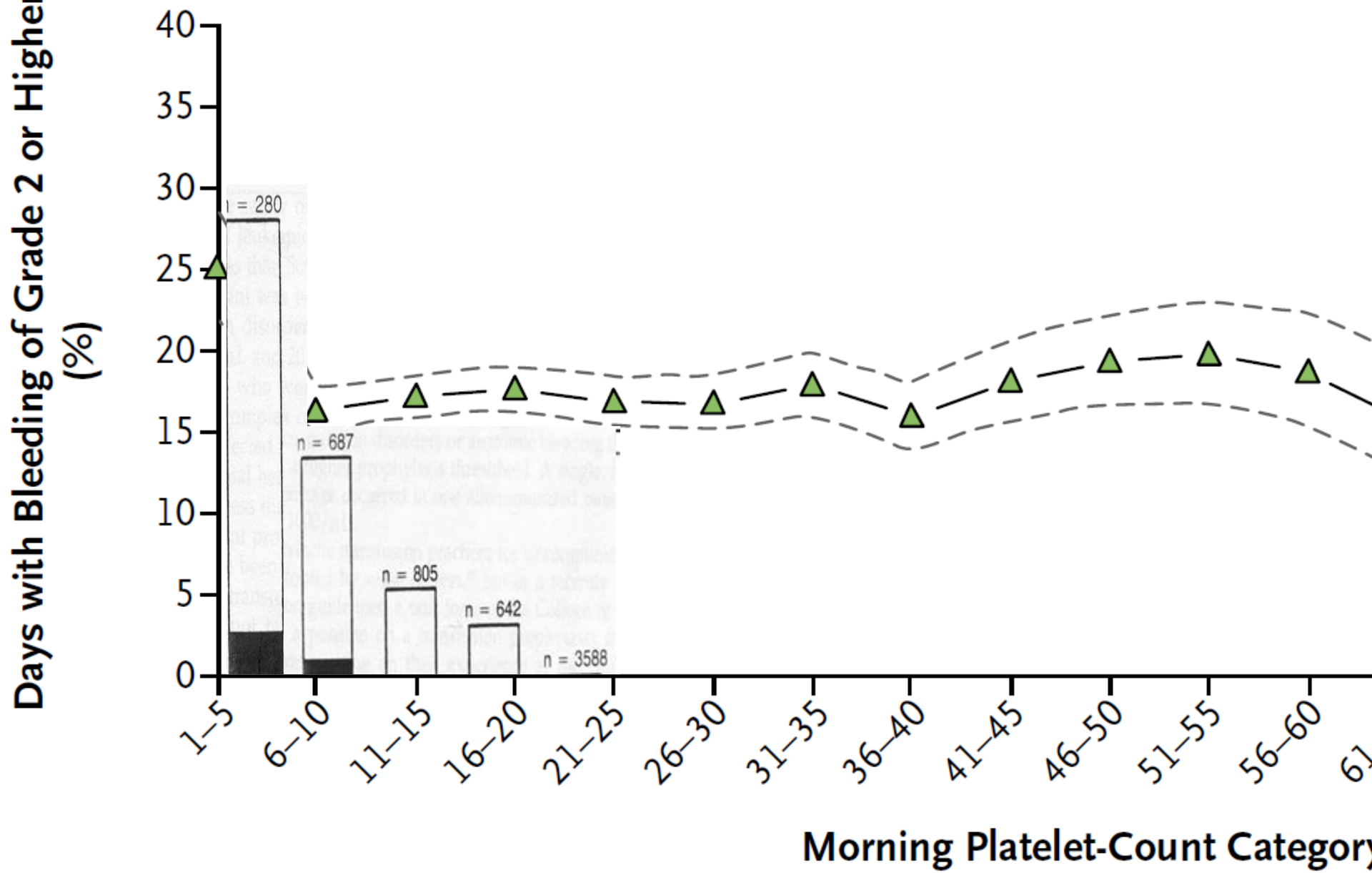


Figure 1. Days with Bleeding of Grade 2 or Higher in All Three Treatment Groups, According to Morning Platelet-Count Categories.

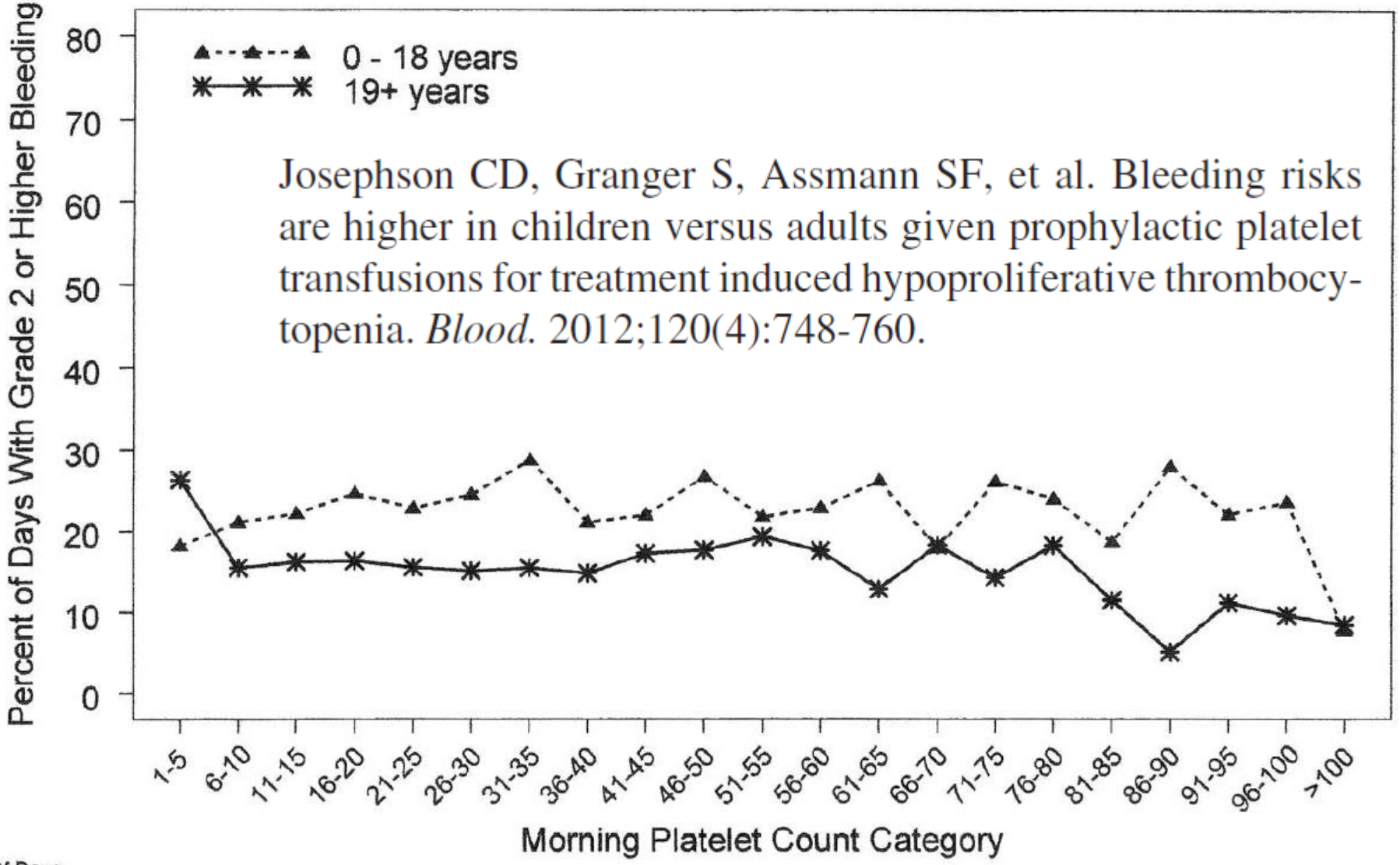
The percentage of days on which patients had bleeding of grade 2 or higher is shown, along with the associated 95% confidence intervals (dashed lines), according to the morning platelet-count category. Data are based on the 24,309 days during the study period on which patients had both a morning platelet count and information on bleeding of grade 2 or higher. Each patient-day was treated as a separate unit of analysis. Analyses were adjusted to take into account that for each patient, the results on various days may be correlated. The interaction between treatment group and morning platelet-count category was not significant, indicating that the effect of the morning platelet-count category did not differ significantly among the three treatment groups; therefore, the data from all three groups are combined.


Days with Bleeding of Grade 2 or Higher (%)
40
35
30
25
20
15
10
5
0
Grade 0 no bleeding
Grade 1 petechial bleeding;
Grade 2 mild blood loss (clinically significant);
Grade 3 gross blood loss, requires transfusion (severe);
Grade 4 debilitating blood loss, retinal or cerebral associated with fata
No bleeding or grade 1 30 32
Grade 2 58 59
Grade 3 9 7
Grade 4 3 2
1–5
6–10
11–15
16–20
21–25
26–30
31–35
36–40
41–45
46–50
51–55
56–60
Morning Platelet-Count Category
No. of Days
652 3240 3843 3194 2449 1976 1501 1182 1009 774 677 513



No. of Days	652	3240	3843	3194	2449	1976	1501	1182	1009	774	677	513

PLADO subset analysis



Josephson CD, Granger S, Assmann SF, et al. Bleeding risks are higher in children versus adults given prophylactic platelet transfusions for treatment induced hypoproliferative thrombocytopenia. *Blood.* 2012;120(4):748-760.

No. Of Days	1-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70	71-75	76-80	81-85	86-90	91-95	96-100	>100
0 - 18 yrs	88	475	642	533	457	352	282	228	196	150	143	114	88	84	73	67	43	43	41	34	473
19+ yrs	564	2765	3201	2661	1993	1624	1219	954	813	624	534	399	321	274	225	165	149	119	99	105	896

Clinical Practice

- How many people use a prophylactic platelet transfusion threshold of:
  - 0
  - 5,000
  - 10,000
  - 15,000
  - 20,000
  - >20,000

Learning Objectives

- Define major, minor, and trivial hemorrhage
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Platelet Transfusion
Indications - Before Procedures

- Bone marrow aspiration/biopsy
- Liver biopsy
- LP
- Central line placement
- Chest physical therapy

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- Bone marrow aspiration/biopsy
- Liver biopsy
  - Transjugular
  - Trans-cutaneous
- LP
- Central line placement
- Chest physical therapy

Platelet Transfusion
Indications - Before Procedures

- Bone marrow aspiration/biopsy
- Liver biopsy
- Lumbar puncture
  - In general
  - With circulating blasts
- Central line placement
- Chest physical therapy

LP complications by platelet count

Platelet	LP (n)	Comps	95% Conf Interval
1-5	6	0	0-40%
6-10	23	0	0-13%
11-20	170	0	0-2.1%
21-30	234	0	0-1.5%
31-40	235	0	0-1.5%
41-50	273 (742)	0	0-1.3% (0-0.5%)
51-100	858	0	0-0.4%
>100	3424	0	0-0.1%
Total	5223	0	0-0.1%

No serious complications were observed at any platelet count.

Howard et al. JAMA 2000

Does thrombocytopenia increase the risk of LP complications?

- Platelets > 20,000 – safe
- Platelets 11,000 to 20,000 – probably safe
- Platelets ≤ 10,000 – safety unknown (29 observations of safe LP at platelet counts of 1 to 10,000 not sufficient to document safety)

LP complications by platelet count

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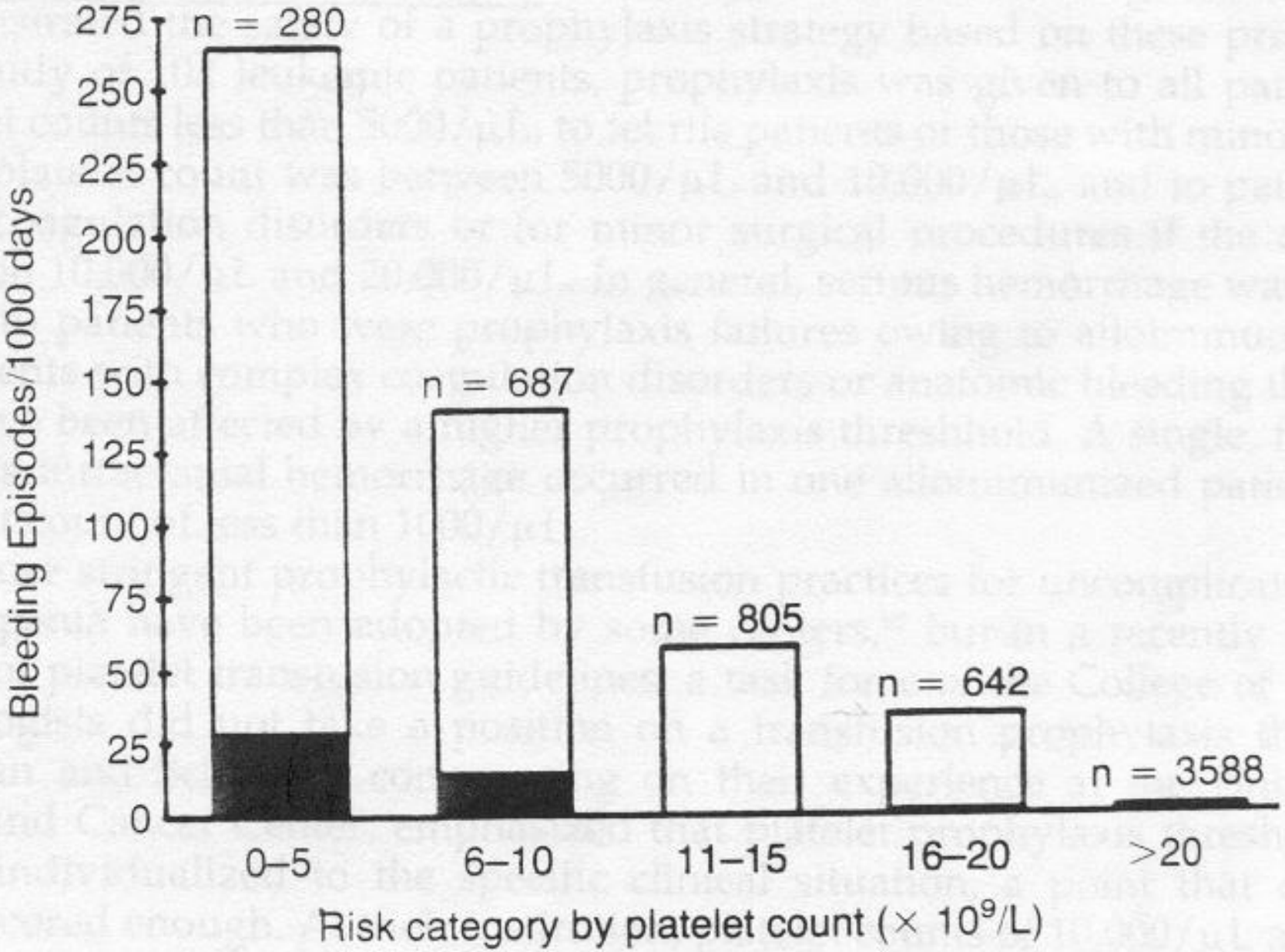
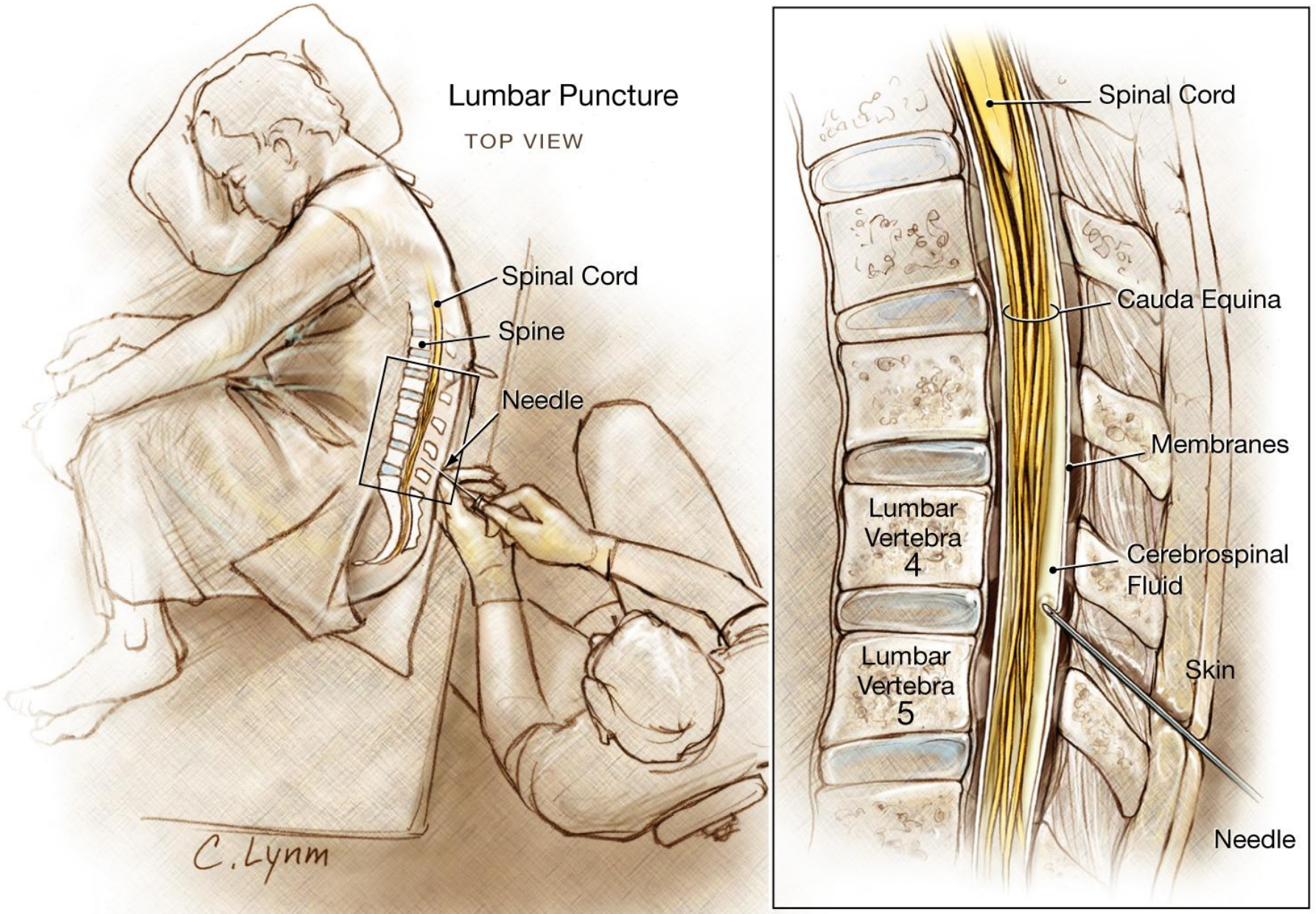
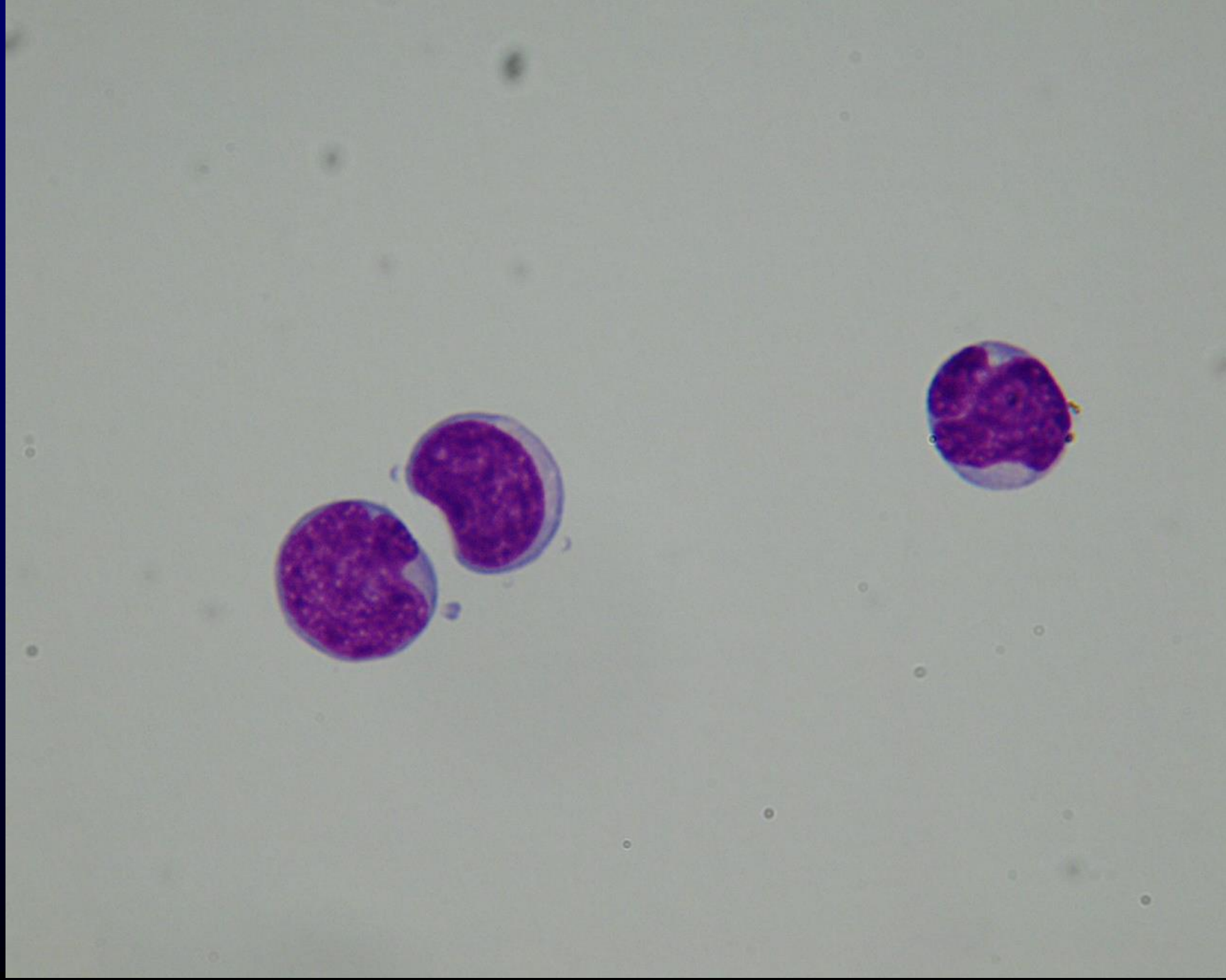
Howard et al. JAMA 2000

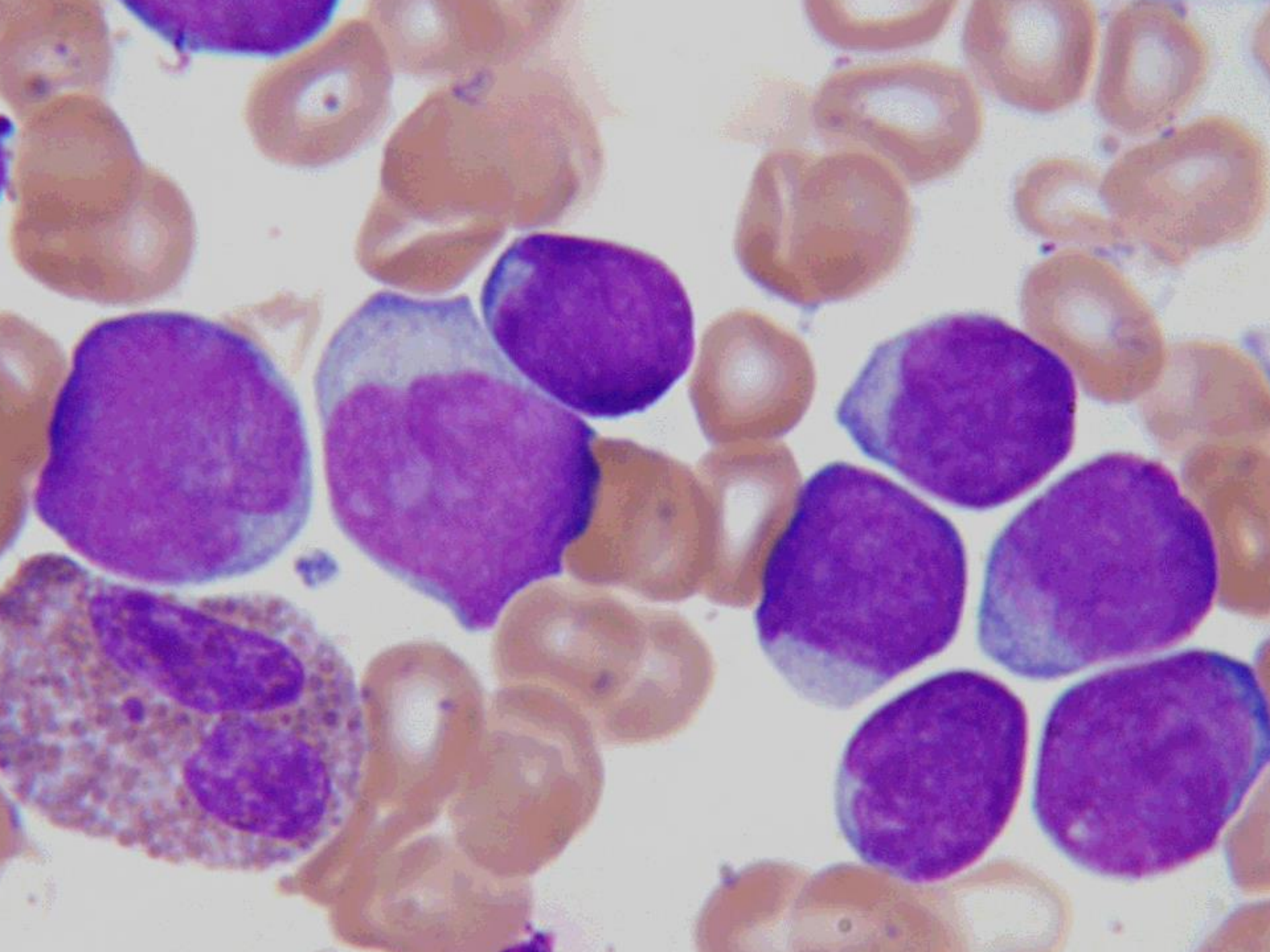


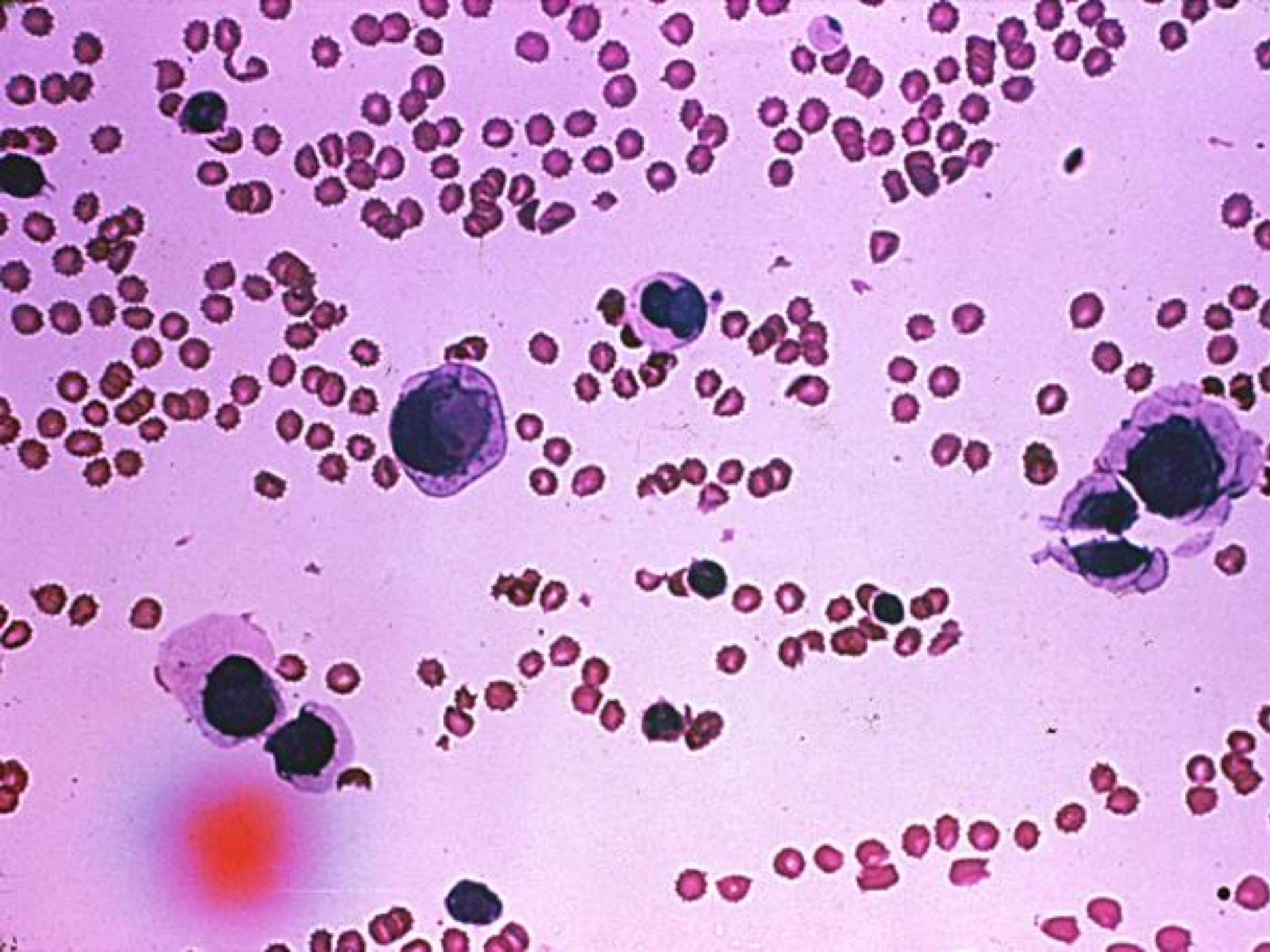
ure 2. Relationship of bleeding risk to platelet counts in 102 leukemia patients g
phylactic platelet support as described by Gmur. Open bars represent minor blee



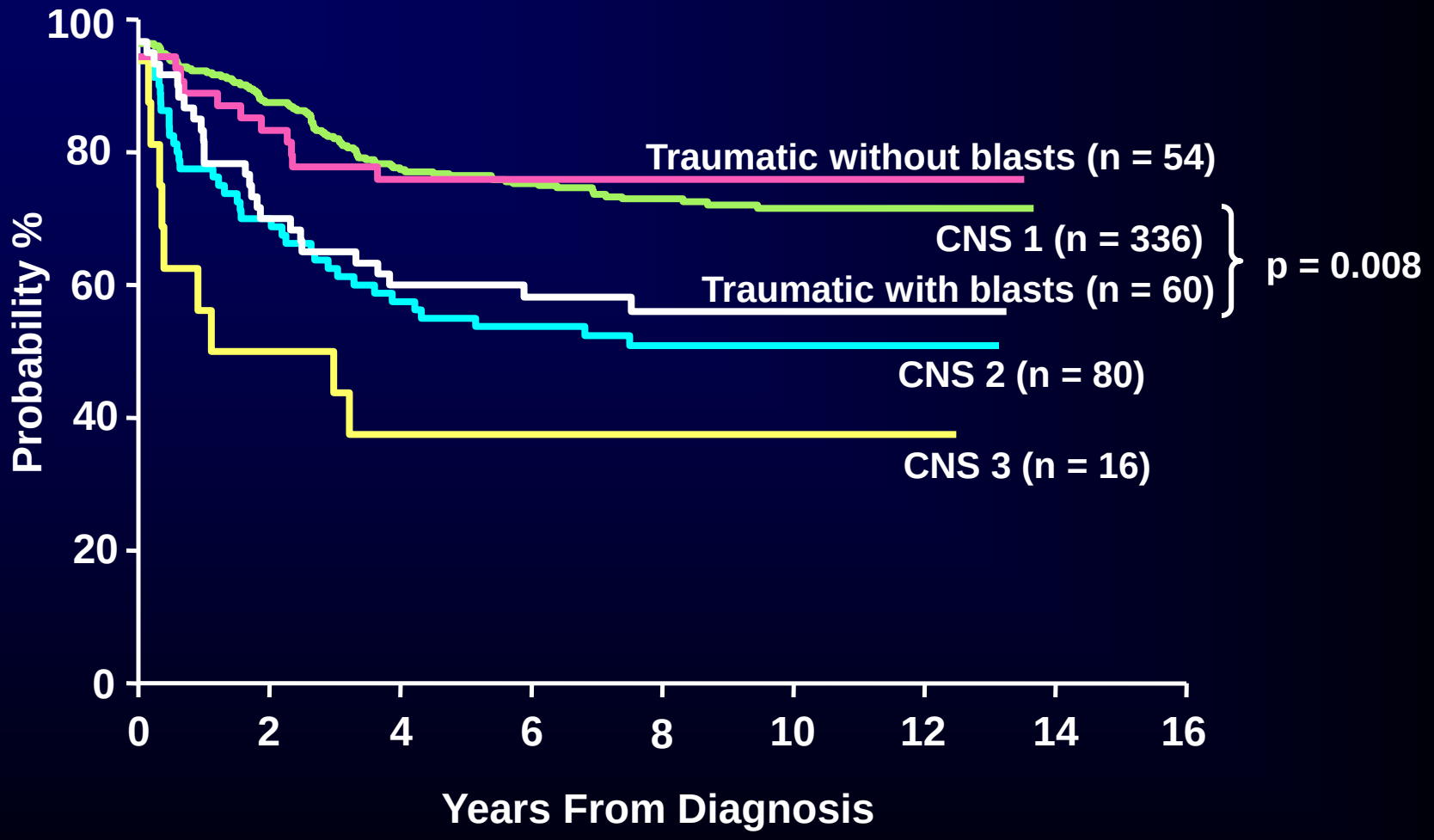
JAMA. 2002;288:2070.





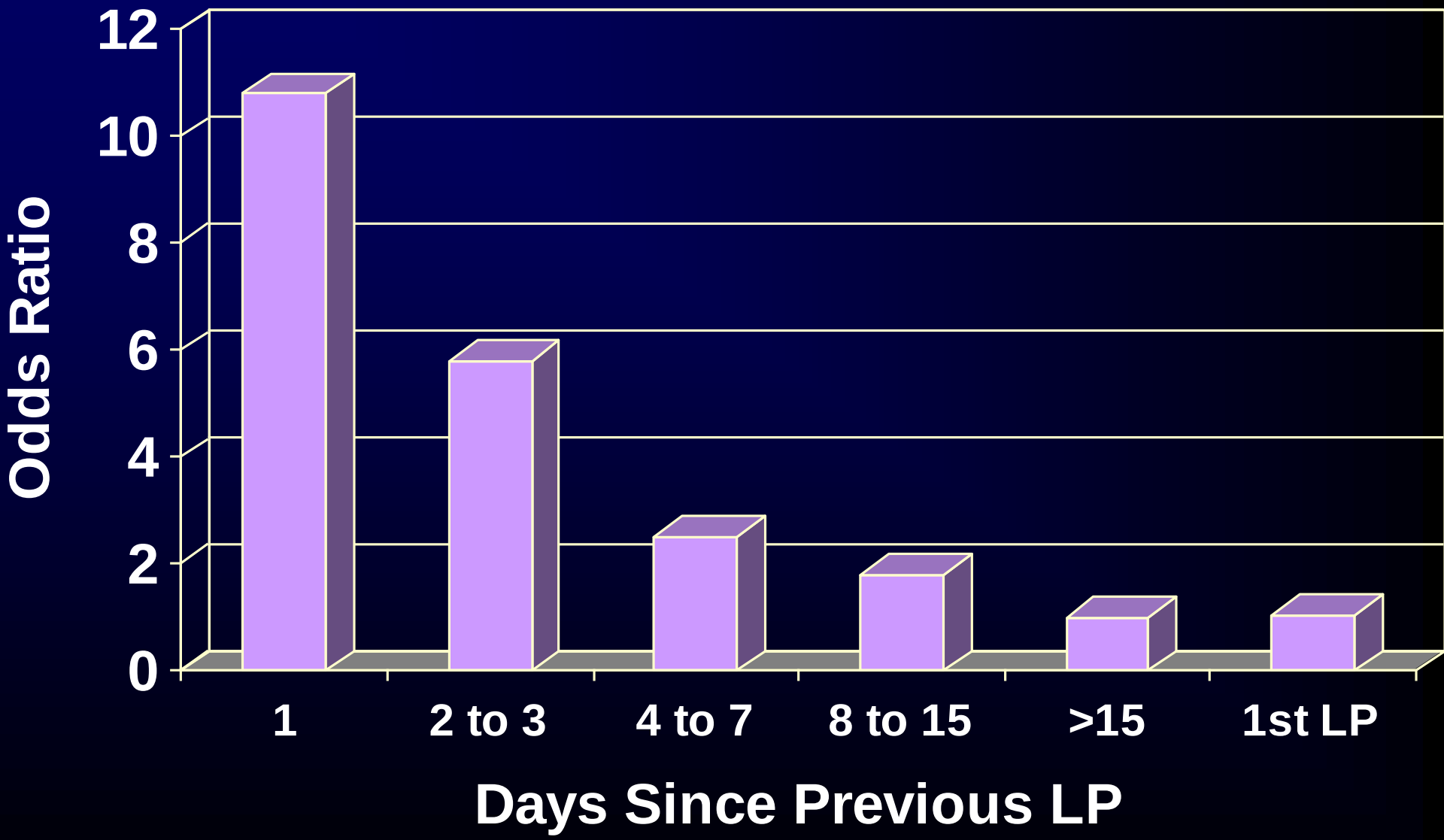


Studies XI and XII
EFS According to CNS Status



Gajjar, A. et al. Blood 2000;96:3381-3384

Odds of traumatic/bloody LP when performed after a previous LP



Unmodifiable Risk Factors for Traumatic Lumbar Puncture

Risk factor	Odds Ratio
Race (black versus white)	1.5
Age (<1 year versus ≥ 1 year)	2.6
Era (early versus late)	1.4
Prior traumatic LP	1.6

Howard et al. JAMA 2002

Table 2. Effects of Platelet Count at Lumbar Puncture (LP) on Tr
Pediatric Patients With Acute Lymphoblastic Leukemia*

Platelet Count, $\times 10^3/\mu L$	No. of LPs	Traumatic LP	
		No. (%)	Odds Ratio (95% CI)†
1-25	382	171 (45)	1.8 (1.3-2.4)
26-50	664	271 (41)	1.4 (1.1-1.8)
51-75	513	191 (37)	1.5 (1.1-1.9)
76-100	353	121 (34)	1.4 (1.1-1.9)
>100	3594	855 (24)	1.0
All LPs with evaluable platelet counts‡	**5506**	**1609** (29)	. . .

*CI indicates confidence interval; ellipses, data not applicable. See asterisk foot
†See dagger footnote of Table 1.
‡Of the 5609 LPs, 103 did not have an associated evaluable platelet count.

Modifiable Risk Factors (with OR) for Traumatic Lumbar Puncture

Modifiable risk factor	Odds ratio
• Platelet count 0-25,000	1.8
• Platelet count 26-50,000	1.4
• Platelet count 50-75,000	1.5
• Platelet count 75-100,000	1.4
• Platelet count >100,000	1
• Practitioner experience	1.4
– (least versus most, 200 LPs)	

Howard et al. JAMA 2002

Risk Factors for Traumatic LP

Multivariable analysis

Factor	OR
Race (B vs W)	1.54*
Age (<1 vs ≥1)	2.37*
Era (early/late)	1.52*
Platelet 0-25	1.68*
Platelet 26-50	1.43*
Platelet 51-75	1.43*
Platelet 76-100	1.42*

Canadian C17 Guidelines
Platelet Transfusion

Children's Cancer
& Blood Disorders

Guideline for Platelet Transfusion Thresholds for Pediatric Hematology / Oncology Patients

Complete Reference Guide

The C17 Guidelines Committee

Grade of Recommendation	Benefit vs Risk and Burdens	Methodology	Implications
1C Strong recommendation, poor quality evidence	Desirable effects clearly outweigh undesirable effects or *vice versa*	Evidence of at least one critical outcome from observational studies, case series or RCTs with flaws	Apply to most patients in many circumstances Further research would be helpful
2A Weak recommendation, high quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from RCTs without important flaws or Exceptionally strong evidence from observational studies	Best action may depend on circumstances or patient or society values Further research unlikely to change recommendation
2B Weak recommendation, moderate quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important flaws or Very strong evidence from observational studies	Best action dependent on patient circumstances or patient or society values Further research may change recommendation
2C Weak recommendation with poor quality evidence	Desirable effects closely balanced with undesirable effects	Evidence of at least one critical outcome from observational studies, case series or RCTs with serious flaws	Other alternatives may be equally reasonable Further research very likely to change recommendation

	Recommendation	Evidence*
Threshold for patients requiring a lumbar puncture	Threshold for stable patients requiring a lumbar puncture to receive prophylactic platelet transfusions is 20 $x10^9$/L. **It is also recognized that some may be uncomfortable with a threshold of 20 $x10^9$/L because of the potentially devastating consequences of an intraspinal bleed.** Transfusions at a higher level **may** be required for patients with signs of bleeding, high fever, rapid fall in platelet count, concomitant coagulation abnormality, critically ill patients, and those with impaired platelet function (including drug induced). Transfusions at a higher level may be required for patients undergoing invasive procedures (see sections below). **Transfusions at a higher level (>50 x 10^9) are recommended for diagnostic LP for newly diagnosed patients with leukemia to minimize the risk of a traumatic LP.**	2B
Threshold for patients requiring a major invasive procedure	Threshold for stable patients requiring a major invasive surgical procedure to receive prophylactic platelet transfusions is 40-50 $x10^9$/L. Transfusions at a higher level **may** be required for patients with signs of bleeding, high fever, rapid fall in platelet count, hyperleucocytosis , APL , concomitant coagulation abnormality, critically ill patients, and those with impaired platelet function	1C

Reducing traumatic first LP
Recommendations

- Most experienced person available
- Deep sedation
- Transfuse platelets to around 100,000
- IT chemo with first LP
- Best of all… DELAY FIRST LP UNTIL CIRCULATING BLASTS ARE GONE

Delaying the diagnostic LP in children with ALL

Delay of the Diagnostic Lumbar Puncture and Intrathecal Chemotherapy in Children With Acute Lymphoblastic Leukemia Who Undergo Routine Corticosteroid Testing: Tokyo Children's Cancer Study Group Study L89-12

By A. Manabe, M. Tsuchida, R. Hanada, K. Ikuta, Y. Toyoda, Y. Okimoto, K. Ishimoto, H. Okawa, A. Ohara, T. Kaneko, K. Koike, T. Sato, K. Sugita, F. Bessho, Y. Hoshi, M. Maeda, A. Kinoshita, T. Saito, Y. Tsunematsu, and S. Nakazawa

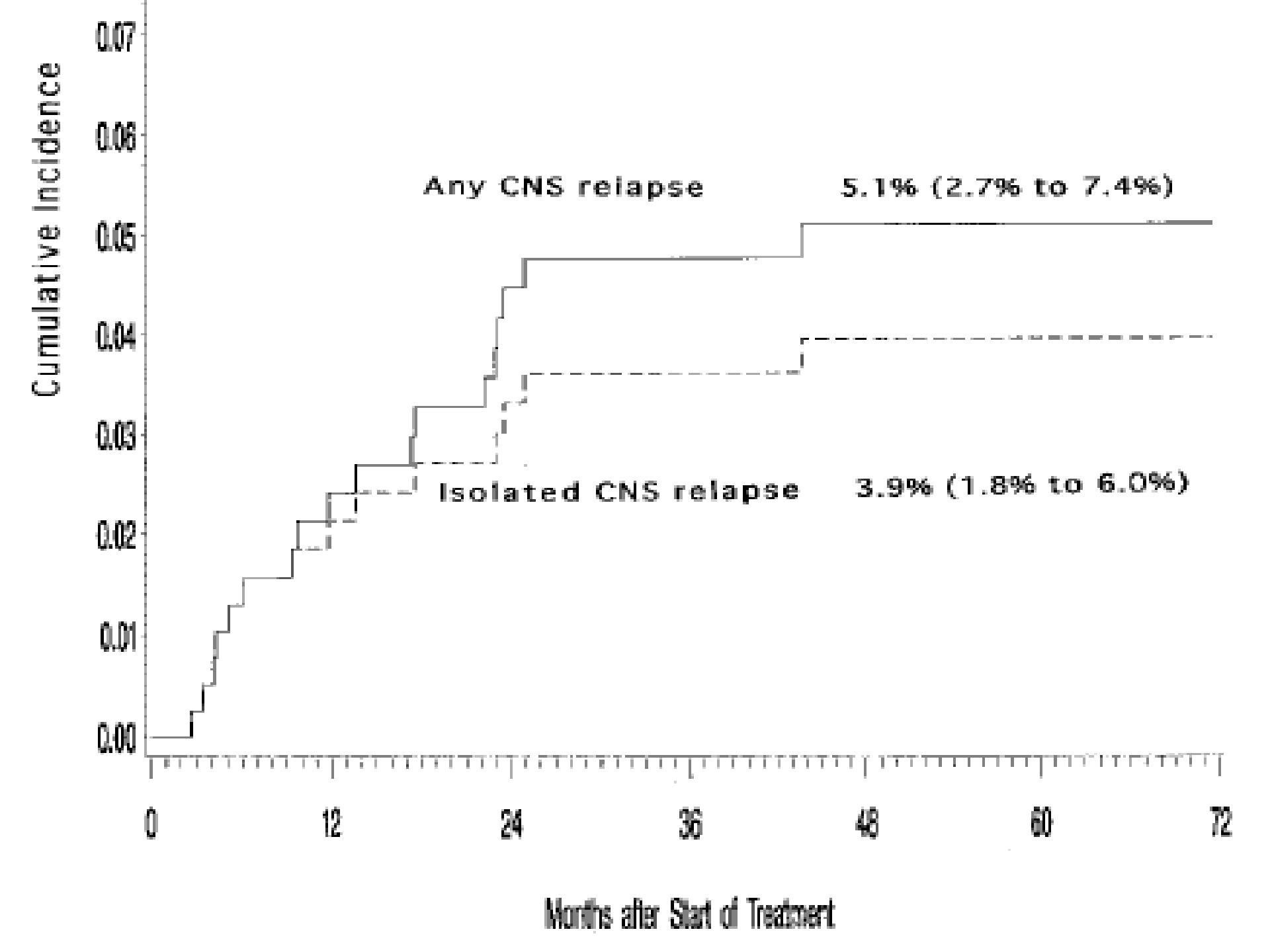
Purpose: To determine the effects of eliminating initial lumbar punctures in 418 consecutively treated children with acute lymphoblastic leukemia (ALL).

Patients and Methods: Patients were enrolled onto a trial conducted in central Japan between 1989 and 1992. Treatment consisted of standard four-drug induction therapy followed by a risk-based intensification phase, reinduction therapy, late intensification, and remission maintenance therapy (total of 104 weeks). The initial lumbar puncture, with an intrathecal injection of chemotherapy, was performed after 1 week of prednisolone sensitivity testing (day 8). End points included response to prednisolone, CNS status at the time of the day 8 lumbar puncture, subsequent adverse events in CNS and bone marrow, and event-free survival (EFS).

Results: The remission induction rate was 93.1% with a 6-year EFS rate (± SE) of 68.7% ± 2.4%, which is similar to historical results for patients who received their diagnostic lumbar puncture and first instillation of intrathecal chemotherapy on day 0. Overall, 84.5% of the patients had good responses to prednisolone, whereas 15.5% had poor responses. Clinical outcome was strikingly better for the good responders (6-year EFS, 74.1% ± 2.5% compared with 40.1% ± 6.4% for patients with poor responses), suggesting that omission of intrathecal chemotherapy did not alter the predictive value of drug sensitivity testing. Eighteen patients experienced CNS relapse as their first adverse event (cumulative risk, 5.1%; 95% confidence interval, 2.7% to 7.4%), coincident with reports from groups using conventional strategies of CNS clinical management. Bleeding into the CSF at the time of the day 8 lumbar puncture was apparent in 29 cases (8.1%), but leukemic blasts were identified in only two.

Conclusion: Delay of the initial lumbar puncture and intrathecal injection of chemotherapy seems to be feasible in children with ALL. Further controlled evaluations are needed to establish the validity of this conclusion.

J Clin Oncol 19:3182-3187.


Cumulative Incidence
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
Any CNS relapse
5.1% (2.7% to 7.4%)
Isolated CNS relapse
3.9% (1.8% to 6.0%)
0
12
24
36
48
60
72
Months after Start of Treatment

Pediatr Blood Cancer 2012;58:23–30

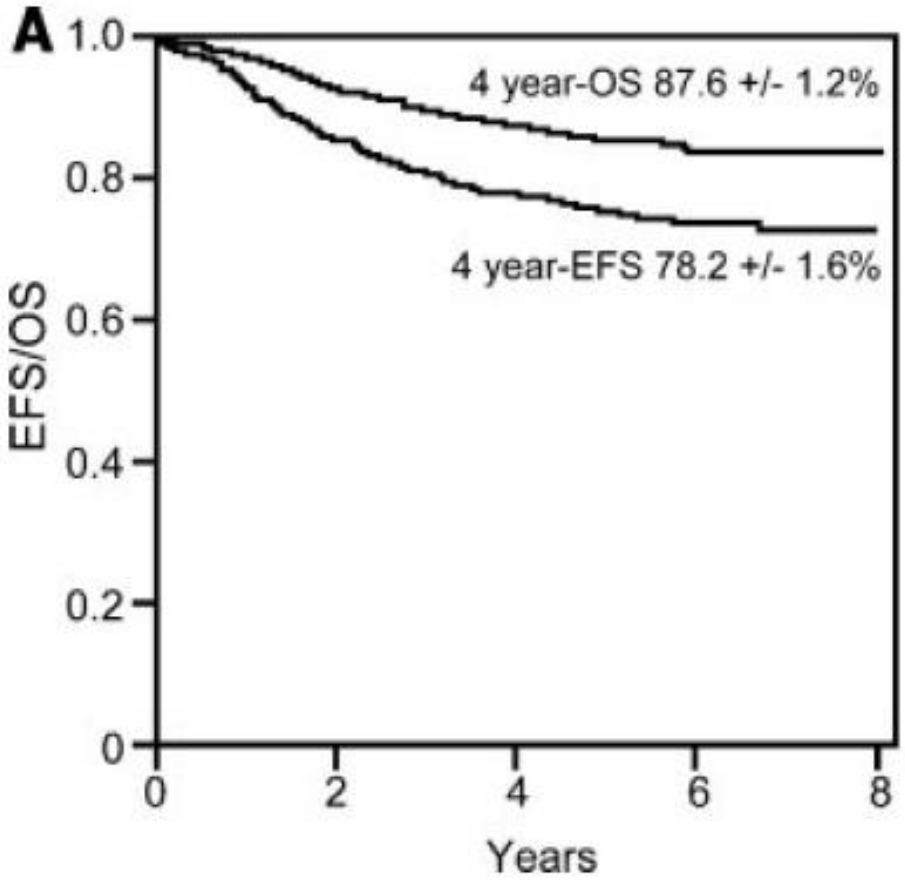
The Utility of Performing the Initial Lumbar Puncture on Day 8 in Remission Induction Therapy for Childhood Acute Lymphoblastic Leukemia: TCCSG L99-15 Study

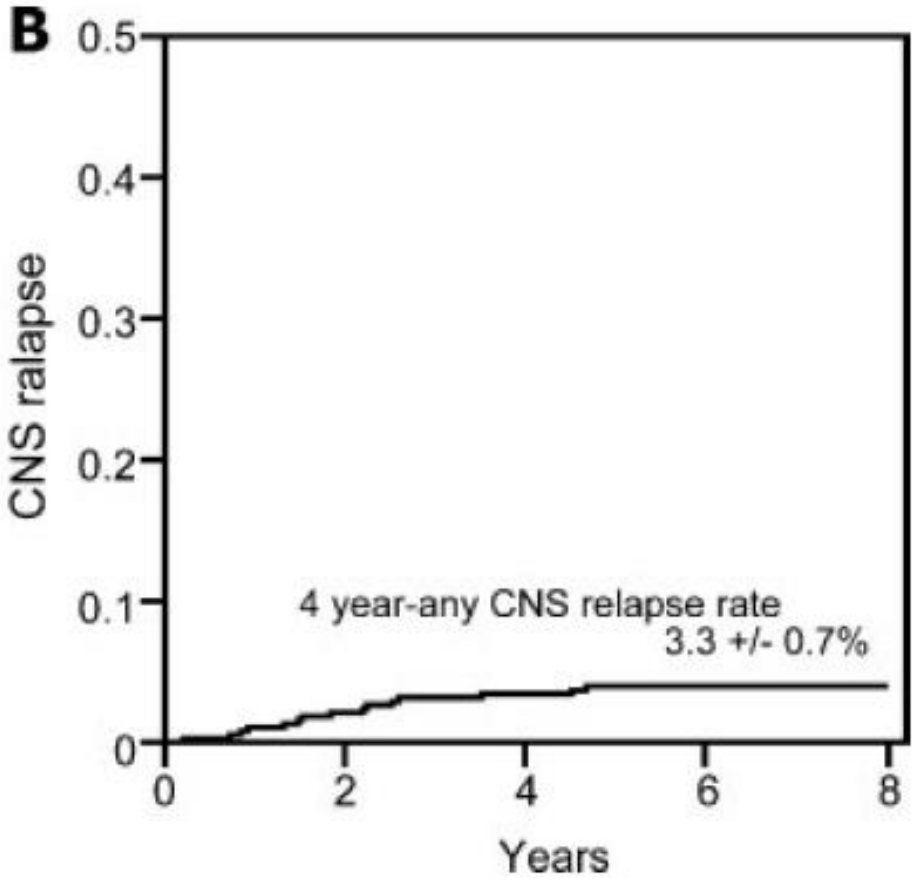
Daisuke Hasegawa, MD, PhD,[1]* Atsushi Manabe, MD, PhD,[1] Akira Ohara, MD, PhD,[2] Akira Kikuchi, MD, PhD,[3] Katsuyoshi Koh, MD,[4] Nobutaka Kiyokawa, MD, PhD,[5] Takashi Fukushima, MD, PhD,[6] Yasushi Ishida, MD, PhD,[1] Tomohiro Saito, MPH,[7] Ryoji Hanada, MD, PhD,[4] Masahiro Tsuchida, MD, PhD,[8] and The Tokyo Children's Cancer Study Group

Background. Traumatic lumbar puncture with leukemic blasts (TLP+), which has been reported to occur 5–10%, in the previous studies, adversely affects the outcome of children with acute lymphoblastic leukemia (ALL). Based on the results from our previous study, we deferred the initial lumbar puncture until day 8 in remission induction therapy in order to reduce the frequency of cases with TLP+. ***Procedure.*** The study was conducted as a prospective cohort study within the Tokyo Children's Cancer Study Group (TCCSG) L99-15 study. Between April 1999 and June 2003, 754 children with newly diagnosed ALL enrolled. The patients received the initial intrathecal chemotherapy after 7 days of prednisolone treatment. The incidence of central nervous system (CNS)-positive (the presence of leukemic blasts in cerebrospinal fluid or cranial nerve palsy) including TLP+ cases and cumulative incidence of CNS relapse were examined. ***Results.*** The incidence of CNS-positive and TLP+ was 2.9% (n = 22) and 0.8% (n = 6), respectively. These incidences were much lower than those in the representative study groups employing the initial IT on day 1. Of 22 patients with CNS-positive, only one patient relapsed in CNS, whereas 22 of the remaining CNS-negative 723 patients suffered from CNS relapse. Overall, event-free survival at 4 year was 78.2 ± 1.6%. Four-year cumulative incidence of any CNS relapse was 3.3 ± 0.7%, which improved from our previous study in spite of limiting the use of cranial irradiation. ***Conclusions.*** Our strategy reduced the frequency of CNS-positive patients who required reinforcement of CNS-directed therapy without compromising overall outcome. Pediatr Blood Cancer 2012; 58:23–30.

Key words: acute lymphoblastic leukemia (ALL); central nervous system (CNS) relapse; chemotherapy; chemotherapy neurotoxicities

EFS, OS and CNS relapse





VOLUME 32 · NUMBER 17 · JUNE 10 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Triple Intrathecal Therapy Alone With Omission of Cranial Radiation in Children With Acute Lymphoblastic Leukemia

Hsi-Che Liu, Ting-Chi Yeh, Jen-Yin Hou, Kuan-Hao Chen, Ting-Huan Huang, Ching-Yi Chang, and Der-Cherng Liang

Listen to the podcast by Dr Pui at www.jco.org/podcasts

Hsi-Che Liu, Ting-Chi Yeh, Jen-Yin Hou, and Der-Cherng Liang, Mackay Medical College, New Taipei; and Hsi-Che Liu, Ting-Chi Yeh, Jen-Yin Hou, Kuan-Hao Chen, Ting-Huan Huang, Ching-Yi Chang, and Der-Cherng Liang, Mackay Memorial Hospital, Taipei, Taiwan.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Der-Cherng Liang, MD, Department of Pediatrics, Mackay Memorial Hospital, No. 92, Sec. 2, Chung-San N. Rd, Taipei 10449, Taiwan; e-mail: dcliang@ms1.mmh.org.tw.

0732-183X/14/3217w-1825w/$20.00

DOI: 10.1200/JCO.2013.54.5020

ABSTRACT

Purpose
To eliminate the toxicities and sequelae of cranial irradiation (CrRT) and to minimize the adverse impact of traumatic lumbar puncture (TLP) with blasts, a prospective study of a modified CNS-directed therapy was conducted in children with acute lymphoblastic leukemia (ALL).

Patients and Methods
Since June 1999, children with newly diagnosed ALL have been treated with triple intrathecal therapy (TIT) alone without CrRT. The first TIT was delayed until the disappearance of blasts from peripheral blood (PB) for up to 10 days of multidrug induction, and CrRT was omitted in all patients. If PB blasts persisted on treatment day 10 (d10), the TIT was then performed.

Results
Of a total of 156 patients, 152 were eligible. Seventeen patients did not have PB blasts at diagnosis. Three fourths of the remaining patients achieved complete clearance of PB blasts by d10. Only hyperleukocytosis at diagnosis showed a significantly lower clearance rate. Six standard-risk patients were upgraded to high risk because of detectable PB blasts on d10. TLPs were encountered in four patients (2.6%), but none were contaminated with lymphoblasts. Neither CNS-2 (less than 5 WBCs/μL with blasts in a nontraumatic sample) nor CNS-3 ($\geq$ 5 WBCs/μL with blasts in a nontraumatic sample or the presence of cranial nerve palsy) was present. The 5-year event-free survival and overall survival rates $\pm$ SE were 84.2% $\pm$ 3.0% and 90.6% $\pm$ 2.4%, respectively. No isolated CNS relapse occurred, but two patients experienced combined CNS relapses. The 7-year cumulative risk of any CNS relapse was 1.4% $\pm$ 1.0%.

Conclusion
Delaying first TIT until circulating blasts have cleared may improve CNS control in children with newly diagnosed ALL and preclude the need for CrRT.

J Clin Oncol 32:1825-1829. © 2014 by American Society of Clinical Oncology

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First LP done only when no peripheral blasts present (latest: day 10 of remission induction therapy with multiple drugs)

Results

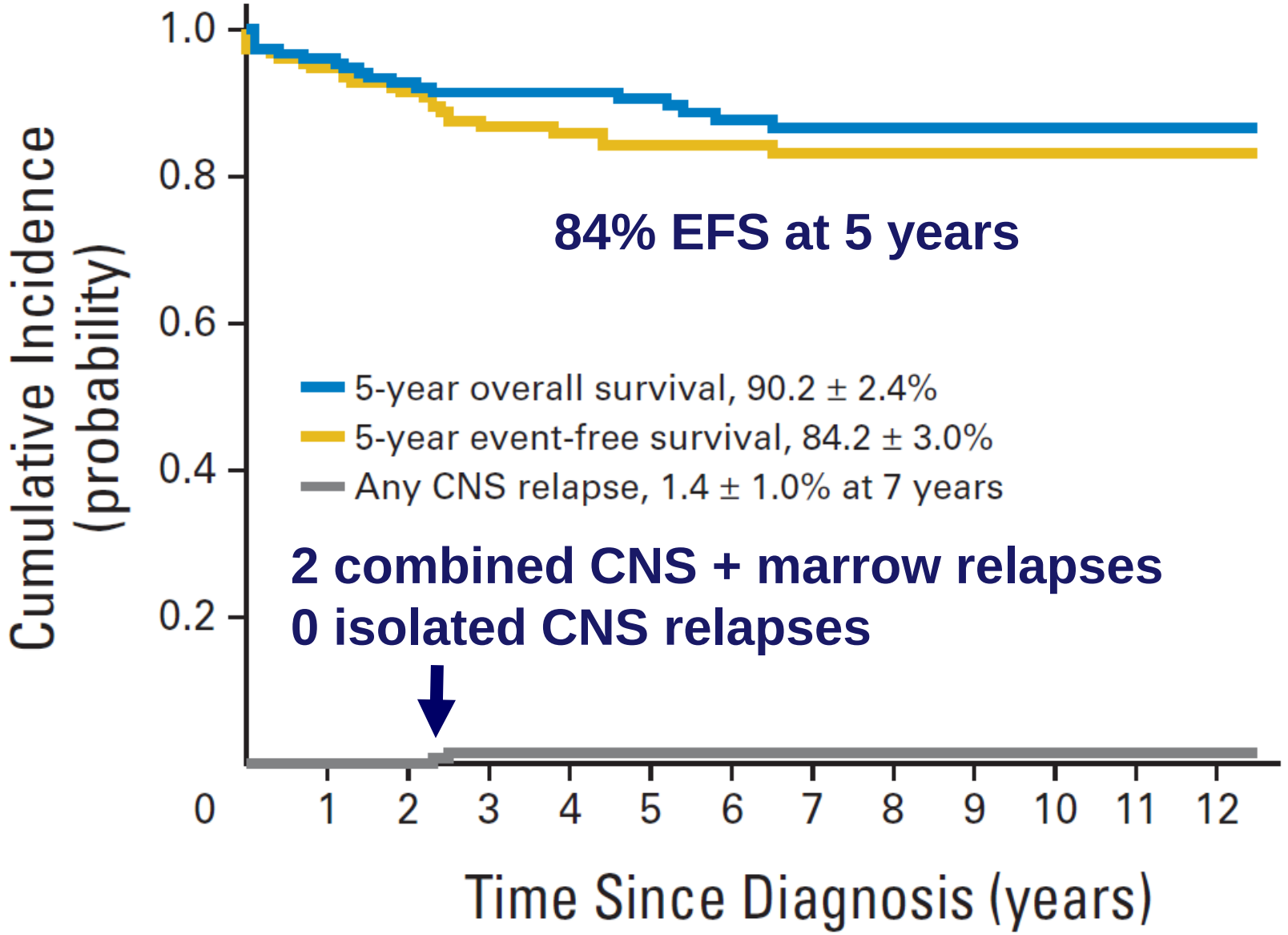
Of a total of 156 patients, 152 were eligible. Seventeen patients did not have PB blasts at

CNS1	**97.4%**
Traumatic without blasts	**2.6%**
CNS2, CNS3	**0.0%**

combined CNS relapses. The 7-year cumulative risk of any CNS relapse was 1.4% ± 1.0%.

Conclusion

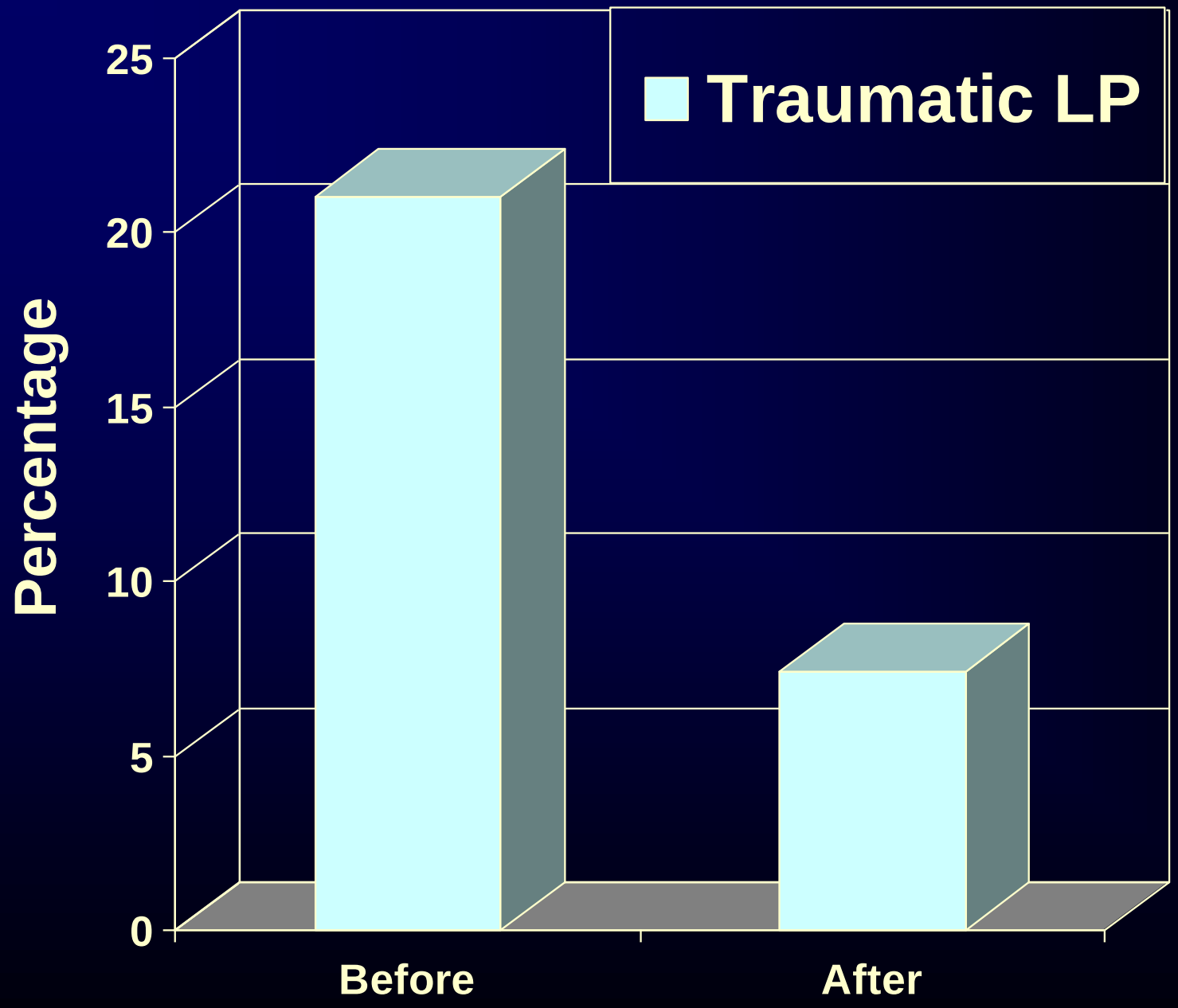
Delaying first TIT until circulating blasts have cleared may improve CNS control in children with newly diagnosed ALL and preclude the need for CrRT.



No. at risk													
Overall survival	152	146	141	124	112	100	86	72	61	50	35	20	14
Event-free survival	152	144	139	119	107	94	83	70	59	48	34	20	14
Any CNS relapse	148	146	141	123	111	100	86	72	61	50	35	20	14

Reducing traumatic first LP
Recommendations

- Most experienced person available
- Deep sedation
- Transfuse platelets to around 100,000
- IT chemo with first LP
- Best of all… DELAY FIRST LP UNTIL CIRCULATING BLASTS ARE GONE


Traumatic LP
Percentage
25
20
15
10
5
0
Before
After

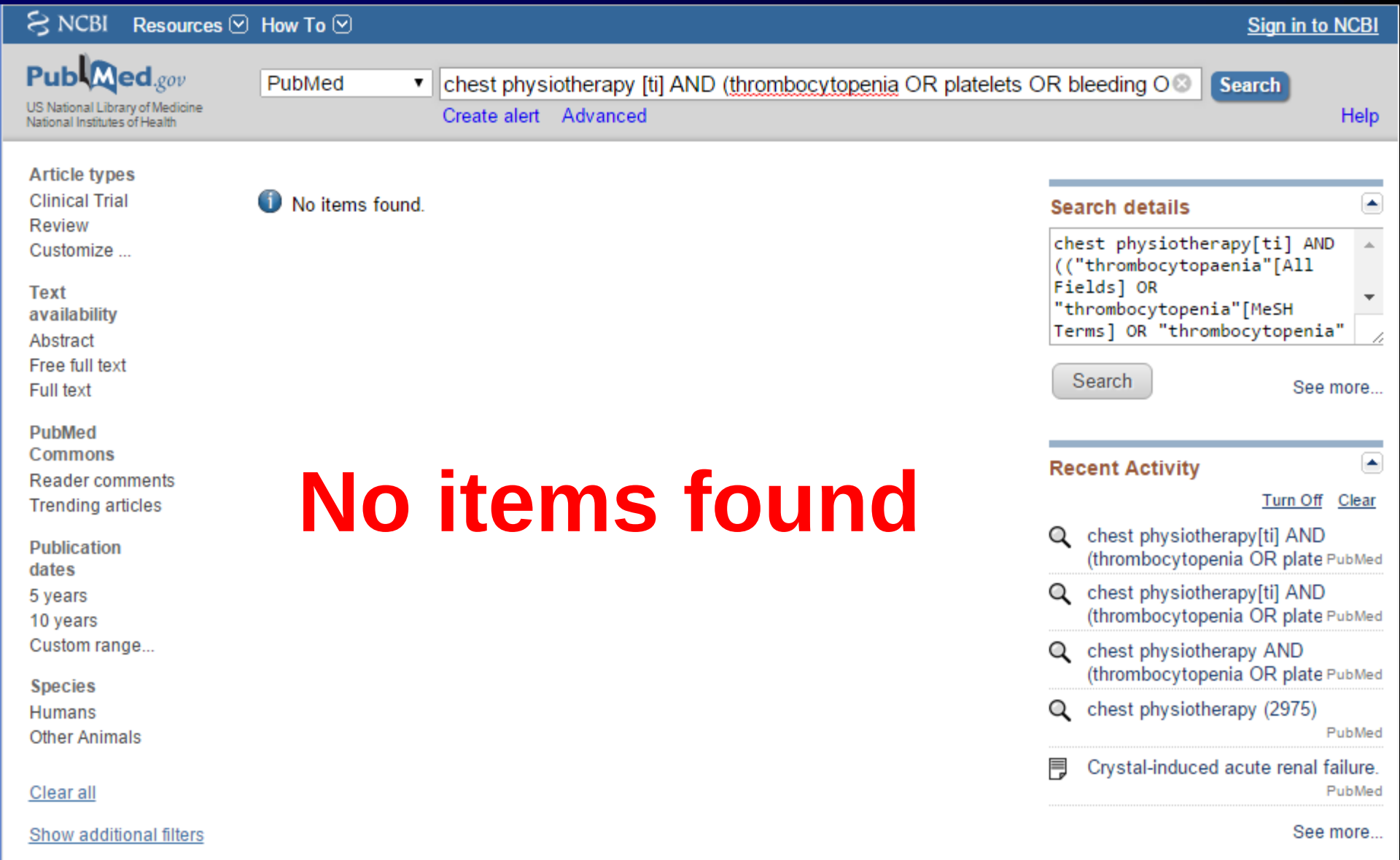
Platelet Transfusion
Indications - Before Procedures

- Bone marrow aspiration/biopsy
- Liver biopsy
- LP
- Central line placement
- Chest physical therapy

Platelet Transfusion
Indications - Before Procedures

- Bone marrow aspiration/biopsy
- Liver biopsy
- LP
- Central line placement
- Chest physical therapy

Chest physiotherapy and thrombocytopenia



Learning Objectives

- Highlight the contents of human blood
- Define major, minor, and trivial hemorrhage
- Review the indications for prophylactic transfusion of platelets in cancer patients
- Identify safe platelet counts for invasive procedures
- Assess the optimal volume of platelets for small children who require transfusion

New Strategies for the Optimal Use of Platelet Transfusions

Morris A. Blajchman,[1] Sherrill J. Slichter,[2] Nancy M. Heddle,[3] and Michael F. Murphy[4]

Table 1. Summary of the main features of the use of platelet transfusions in three multicenter RCTs that have either recently been completed (PLADO), stopped (SToP), or is ongoing (TOPPS) evaluating different strategies for use in thrombocytopenic patients with a hypoproliferative marrow.

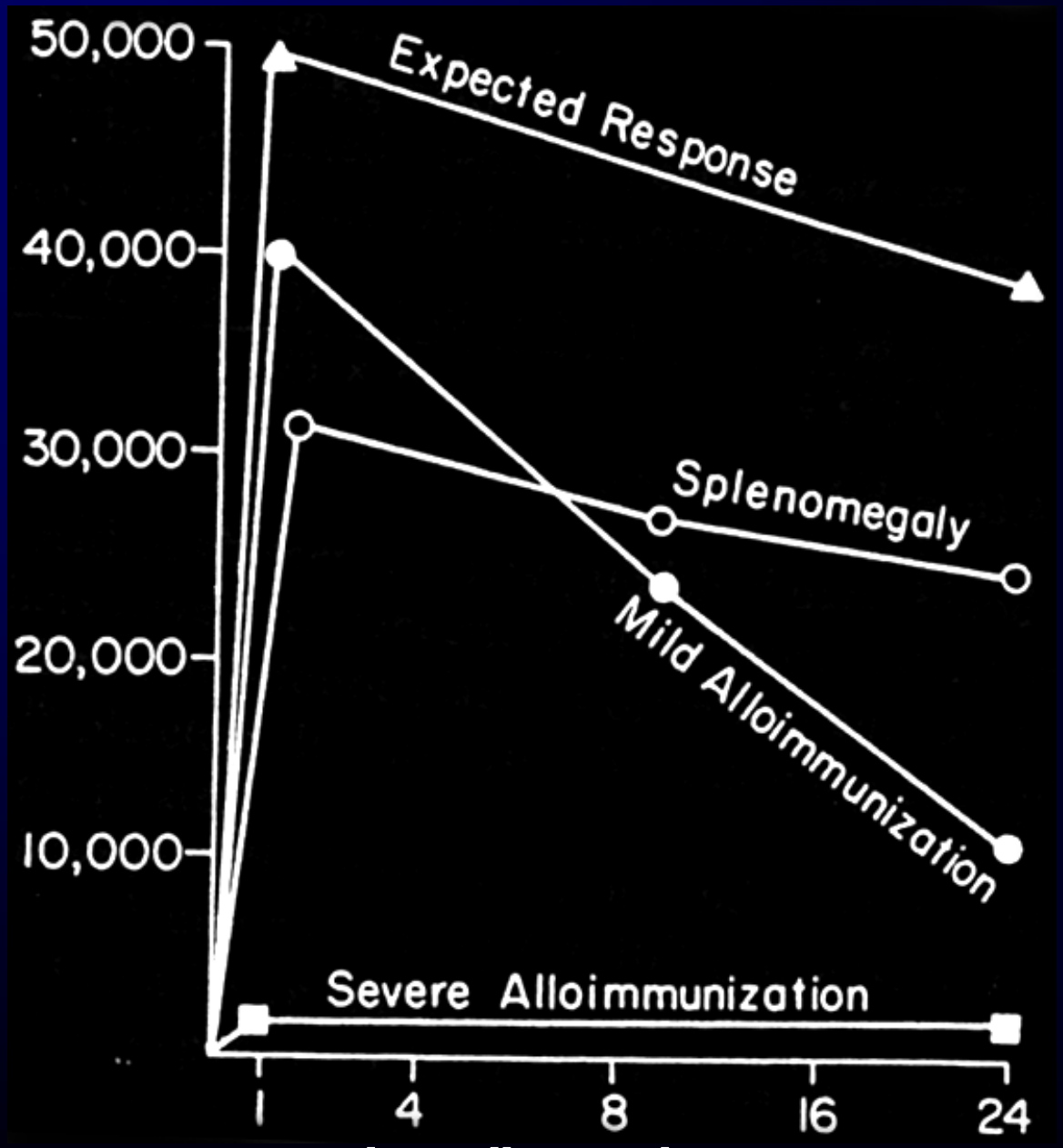
	PLADO	SToP	TOPPS
Type of platelet transfusion intervention	Prophylactic	Prophylactic	Therapeutic vs prophylactic
Primary Endpoint	WHO Bleeding (grade 2 or greater)	WHO Bleeding (grade 2 or greater)	WHO Bleeding (grade 2 or greater)
Projected sample size, n	1350 (3 arms)	270 (2 arms)	300 (2 arms)
Arm 1 intervention	1.1×10^{11} platelets/m^2	1.5 to 2.9×10^{11} platelets	Prophylactic platelet transfusions with a trigger of 10×10^9/L
Arm 2 intervention	2.2×10^{11} platelets/m^2	3.0 to 6.0×10^{11} platelets	Therapeutic platelet transfusions only
Arm 3 intervention	4.4×10^{11} platelets/m^2	N/A	N/A
Study Status	Concluded; data being analyzed	Stopped by DSMB (n = 130)	Ongoing

Abbreviations: PLADO, Prophylactic PLAtelet Dose study; SToP, Strategies for the Transfusion of Platelets study; TOPPS, Trial Of Prophylactic Platelets Study; N/A, not applicable; DSMB, data safety monitoring board; WHO, World Health Organization.

How many platelets shall I give?

- **Bleeding: until bleeding stops or >100,000 platelet count**
- **Prophylaxis: 2 x 10^{11} per m^2 of body surface area (BSA)**
- **One pheresis session leads to collection of 3 to 9 x 10^{11} platelets, which can be split into 2 (sometimes even 3) units**
- **1 unit has 3-6 x 10^{11} in 150-400 mL**
- **<1 m^2 BSA: 10-20 mL/kg**
- **1 m^2 BSA or more: 1 unit**

Response to Platelet Transfusion



Major points

- Hemorrhage should be rapidly treated
- Most patients: prophylactic platelet transfusion when the platelets <10,000
- Higher or lower thresholds in special situations – RISK vs. BENEFITS
- No premedication with antihistamines or antipyretics
- One pheresed unit (4-6 buttons) for most patients, 10-20 mL/kg for small children

EXPERT REVIEWS

Supportive medical care for children with acute lymphoblastic leukemia in low- and middle-income countries

Expert Rev. Hematol. Early online, 1–14 (2015)

Francesco Ceppi[1], Federico Antillon[2], Carlos Pacheco[3], Courtney E Sullivan[4], Catherine G Lam[4,5], Scott C Howard[6] and Valentino Conter*[4,7]

[1]*Division of Hematology/Oncology, The Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada*
[2]*National Pediatric Oncology Unit, and Francisco Marroquín Medical School, Guatemala City, Guatemala*

In the last two decades, remarkable progress in the treatment of children with acute lymphoblastic leukemia has been achieved in many low- and middle-income countries (LMIC), but survival rates remain significantly lower than those in high-income countries. Inadequate supportive care and consequent excess mortality from toxicity are important causes of treatment failure for children with acute lymphoblastic leukemia in LMIC. This article summarizes practical supportive care recommendations for healthcare providers practicing in LMIC, starting with core approaches in oncology nursing care, management of tumor lysis syndrome and mediastinal masses, nutritional support, use of blood products for anemia and thrombocytopenia, and palliative care. Prevention and treatment of infectious diseases are described in a parallel paper.

KEYWORDS: acute lymphoblastic leukemia • chemotherapy • low-income country • middle-income country • oncology nursing • pediatrics • supportive care

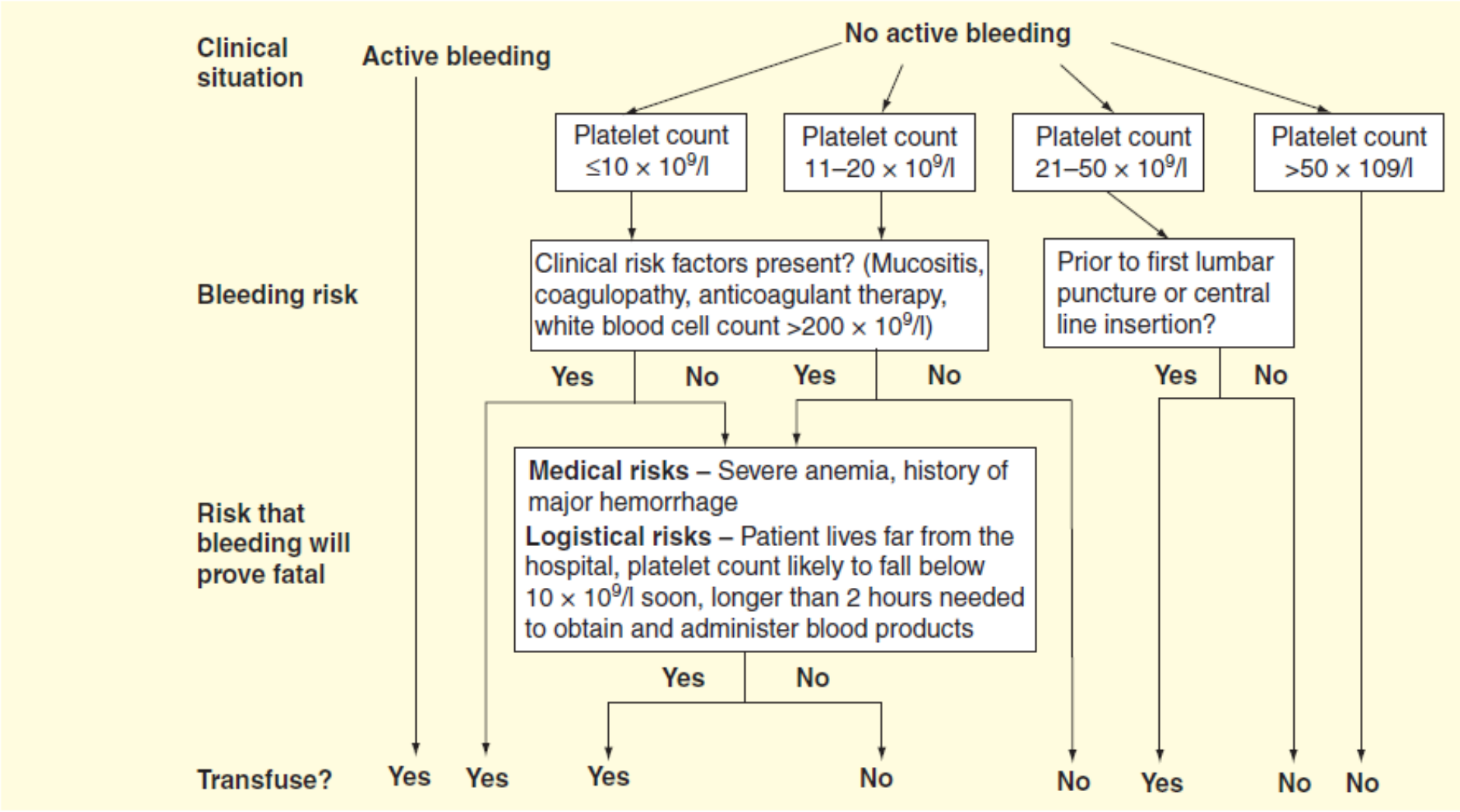


Figure 3. Platelet transfusion algorithm.
If transfusion reaction occurs: Diphenhydramine 0.5–1 mg/kg PO or IV (max 50 mg), acetaminophen 10–15 mg/kg PO (max 6
and hydrocortisone 2–4 mg/kg IV (max 250 mg/dose).