Check for updates

Platelets: Testing, Dosing and the Storage Lesion—Recent Advances

Richard M. Kaufman

The demand for platelet transfusions continues to grow. Several complementary approaches that may help meet this demand in the future are reviewed. First, platelet bacterial testing is beginning to allow the extension of platelet storage beyond 5 days. Studies are also underway aimed at better preserving viability and function during *ex vivo* platelet storage: additive solutions and other approaches are being developed to try to negate the "platelet storage lesion." Finally, new approaches to dosing platelets may help extend the limited supply.

The demand for platelet transfusions continues to grow. Several complementary approaches may help meet this demand in the future. First, platelet bacterial testing is beginning to allow the extension of platelet storage beyond 5 days. Studies are also underway aimed at better preserving viability and function during ex vivo platelet storage: additive solutions and other approaches are being developed to try to negate the "platelet storage lesion." Finally, new approaches to dosing platelets may help extend the limited supply.

Screening Platelets for Bacteria

Over the years, improvements in donor screening nearly eliminated hepatitis B virus, hepatitis C virus and HIV from the US blood supply.[1,2] As the transfusion-transmission rates of these agents dropped, platelet bacterial contamination assumed a new prominence as the most frequent infectious risk of transfusion. Unlike red cells, which are stored under refrigeration, platelets are best stored at room temperature. If platelets are refrigerated prior to being transfused, they are rapidly cleared from the recipient's circulation.[3] While room temperature storage allows transfused platelets to circulate *in vivo*, it has the downside of promoting bacterial growth. Because of this risk, platelet storage is ordinarily limited to only 5 days, making platelet inventory management extremely challenging.

In the 1990s, numerous studies demonstrated that contaminating bacteria, usually representing skin flora from the donor, could be cultured out of approximately 1/3000 platelet units.[4] Clinically apparent septic transfusion reactions were thought to occur following ~1/25,000 platelet transfusions, although there is considerable uncertainty around this point estimate.[4] In 2002, an open letter calling for immediate action to reduce the risk of platelet bacterial contamination[5] led to the proposal of AABB standard 5.1.5.1. The standard states:

Correspondence: Richard Kaufman, MD, Brigham and Women's Hospital, 75 Francis St., Blood Bank; Amory 2-260, Boston MA 02115; Phone 617-732-4749; Fax 617-277-9013; Email rmkaufman@partners.org

> 5.1.5.1 The blood bank or transfusion service shall have methods to limit and detect bacterial contamination in all platelet components. Standard 5.6.2 applies [skin disinfection].[6]

All AABB accredited blood banks were required to meet standard 5.1.5.1 by March 1, 2004. How this standard is being met varies by facility. As of now, three culture-based bacterial detection systems are licensed in the US for quality control use: BacT/Alert (BioMerieux), eBDS (Pall) and Scansystem (Hemosystem). "Quality control" in this context means that the test is licensed to verify that the platelet collection process does not introduce contaminating bacteria more frequently than a predefined rate. These tests are not yet licensed as "release tests," which by definition are used to confirm that a platelet product being issued is not contaminated with bacteria. The BacT/ALERT system, used by most centers performing culture-based screening, works by continuously monitoring for bacterial production of CO_2 within culture bottles. Platelet products are generally sampled on day 1 after collection. The samples are cultured for a period of time, typically 24 hours, and if the cultures fail to produce abnormal levels of CO_2, the product is released into inventory. Both aerobic and anaerobic cultures may be performed, although it is known that aerobic organisms cause the vast majority of septic reactions. The Pall eBDS (enhanced bacterial detection system) detects oxygen consumption by aerobic bacteria. An oxygen sensor is used to measure the residual O_2 in the air above a platelet sample 24 hours after sampling. The Hemosystem Scansystem also requires a culturing step, but this device detects bacteria directly by using a solid-phase fluorescent cytometric method. In the US, these systems are only used to test single donor apheresis platelet units. By current US Food and Drug Administration (FDA) rule, whole blood–derived platelets must be pooled prior to issue as opposed to prestorage.[7-9] Individually culturing multiple concentrates comprising a single platelet dose would be prohibitively cumbersome and expensive, so for whole blood–derived platelets, non-licensed, non-culture methods such as pH and glucose testing (using a dipstick

Downloaded from http://ashpublications.net/hematology/article-pdf/2006/1/492/1091730/492_496ash.pdf by guest on 08 June 2024

or automated analyzer) and Gram staining are performed. However, the sensitivity and specificity of these non-culture methods is inferior to culture-based methods.[10,11] Prestorage pooling of whole blood–derived platelet concentrates is routinely done in a number of countries. Studies now in progress, combined with data from other countries, will likely lead to licensing of prestorage pooled whole blood–derived platelets in the US, thus allowing an equivalent level of surveillance for all platelet products.

Impact of Bacterial Testing

Standard 5.1.5.1 has been in effect long enough to begin to assess its impact on platelet transfusion safety. **Table 1** summarizes three large-scale surveillance studies of septic reactions that were performed prior to the implementation of standard 5.1.5.1: a Johns Hopkins University study,[12] the French BACTHEM study,[13] and the US BaCon study.[14] In the Hopkins and BACTHEM studies, the risk of a clinically apparent septic transfusion reaction ranged from 1/2500-1/31,000 platelet transfusions. Fatalities were observed following ~1/5-1/10 septic reactions. Bacterial contamination appeared to occur less often with single donor platelets than with pooled random donor platelets.[12,13] The prevalence of septic reactions was dramatically lower in the BaCon study than in the other two studies; it has been argued that the BaCon study was limited by an underestimation bias.[4]

A large post-standard 5.1.5.1 study is also summarized in **Table 1**.[15] Over a 10-month period, apheresis platelets collected at 36 American Red Cross blood centers were cultured 24 hours after collection using the BacT/ALERT system. Products were eligible for release after 12 hours without a positive culture. In all, 350,658 units were tested. There were 226 initially positive cultures (1/1552), of which 68 were confirmed as true positive (1/5157). During the study period, 3 platelet transfusions, screened as negative by BacT/ALERT, resulted in "high probability" septic reactions (1 fatal) due to coagulase-negative *Staphylococcus*. In contrast, over an identical period of time prior to bacterial screening, there were 12 high probability septic reactions (2 fatal). A similar rate of contaminated products was seen in a study by Holme and colleagues, who identified 23 confirmed positives out of 118,067 platelet units tested using the Pall eBDS system (1/5133).[16] Similar contamination rates have also been reported by European centers using the BacT/ALERT system.[17] Overall, culture-based bacterial screening appears to reduce, but not eliminate, the risk of septic reactions. Reducing the risk even further may ultimately require alternative approaches, such as pathogen reduction.[15,18-20]

While the current culture systems have increased platelet safety, there are a number of costs: higher prices for platelets, 1-2% product loss from sampling and 12-30 hour delays in platelet product release, potentially affecting platelet availability.[21] It is hoped that these costs will be offset by the benefits of being able to extend platelet storage beyond the 5-day limit. The FDA has established two criteria by which the shelf life of platelets may be extended up to 7 days. First, products must be stored in containers approved for 7-day storage (these are available). Second, products must test negative for bacteria with an FDA-approved release test. The FDA has issued specific guidelines under which the current bacterial detection devices could be validated for release testing.[22] In post-marketing surveillance studies, cultures will need to be performed following platelet outdating (day 7) to confirm the initial (day 1) negative culture. Approval of a culture-based release test will require demonstrating that a negative day 1 culture will only give rise to a true positive day 7 culture in 1/10,000 cases, with 95% confidence that the actual risk is < 1/5000. (A risk of < 1/5000 would be considered to be lower than the current estimated risk for 5-day platelets.) To achieve this high degree of statistical confidence, a very large study size will be required, approximately 50,000 units. Gambro BCT has initiated such a study, the "Post Approval Surveillance Study of Platelet Outcomes, Release Tested" (PASSPORT) study. In this protocol, apheresis platelets collected using the Spectra or Trima devices are cultured 24 hours after collection using the BacT/ALERT system. Both aerobic and anaerobic cultures are performed. After 24 hours, the products are made available for clinical use with a 7-day shelf life. Any products that outdate are re-cultured on day 8. Fifty thousand outdated products are to be tested.[21]

Downloaded from http://ashpublications.net/hematology/article-pdf/2006/1/492/1091730/492_496ash.pdf by guest on 08 June 2024

Table 1. Prevalence of clinically apparent septic transfusion reactions, before (A) and after (B) implementation of AABB standard 5.1.5.1.

	Study	Septic Reactions		Fatal Septic Reactions	
		Pooled RDPs	SDPs	Pooled RDPs	SDPs
A. Pre-standard 5.1.5.1.					
	Ness et al (Hopkins)[12]	1/2,500	1/13,000	1/16,000	1/67,000
	Perez et al (BACTHEM)[13]	1/14,000	1/31,000	0	1/140,000
	Kuehnert et al (BaCon)[14]	1/100,000	1/100,000	1/500,000	1/450,000
B. Post-standard 5.1.5.1					
	Fang et al[15]	ND	1/117,000	ND	1/350,000

Abbreviations: RDPs, random donor platelets; SDPs, single donor (apheresis) platelets.

Rapid Tests for Bacteria

Because of their high sensitivity (detection limit of 1-10 CFU/mL), culture-based systems are the current gold standard for platelet bacterial detection. However, culturing platelet units is both cumbersome and expensive. Also, platelet cultures use up 4-8 mL of platelet product that would otherwise have gone to the patient, and the 24-hour incubation period shortens an already brief shelf life. Ideally, a sensitive, inexpensive test for bacteria could be performed rapidly on a small volume of platelet product just before issue. Several such tests are under development, although none is licensed as of this writing.[23,24] Current-generation rapid bacterial tests have a turnaround time of a few hours or less, and use < 1 mL of platelet product. They have a lower sensitivity than culture, however—on the order of 10^3-10^4 CFU/mL. In principle, rapid bacterial tests could be used for quality control, as an adjunct to another test e.g., initial culture, or as a stand-alone release test. Licensing criteria for rapid bacterial tests are being developed by the FDA.[25]

The Platelet Storage Lesion

If platelet storage is routinely extended past 5 days, it will be important to understand how well 7-day-old platelets, (or perhaps even older platelets) will function clinically. It has long been recognized that platelet viability and function decline over time, the so-called "platelet storage lesion."[26,27] The most compelling data pointing to damage incurred during platelet storage come from radiolabeling studies in autologous volunteer platelet donors. Most investigations have shown that platelets transfused following storage have a significantly decreased recovery and survival relative to fresh platelets.[26,28,29] For example, day 5 and day 7 platelets have been compared directly in radiolabeling studies. Day 5 platelets were found to have a mean recovery of 63% and a mean survival of 160.8 hours, compared with day 7 platelets, which had a recovery and survival of 53.9% and 133.6 hours, respectively.[30]

Numerous morphologic, biochemical and functional derangements occur during platelet storage. Platelets continue to be metabolically active at room temperature. Products of metabolism such as lactate accumulate, and the pH falls. It has been shown that if the pH drops below 6.0-6.2, survival *in vivo* is severely diminished.[26] Platelets also tend to become activated during storage. Over time, an increasing fraction of platelets in a concentrate will change from a discoid (resting) shape to spherical. Mediators of thrombosis such as β-thromboglobulin and platelet factor 4 accumulate in the storage medium, reflecting granule release. Platelet surface levels of P-selectin (CD62P), another platelet activation marker, also increase during storage. Finally, functional derangements are observed *in vitro*. Platelet aggregation responses to a number of agonists drop significantly during storage. Still, beyond a few extreme cases (e.g., pH < 6.0) the significance of the *in vitro* abnormalities observed following platelet storage remains unclear. First, no *in vitro* test has yet been validated to reliably predict platelet survival *in vivo*.[31] Also, there is good evidence suggesting that many of the platelet storage abnormalities seen *in vitro* are actually reversible upon transfusion.[32]

In practice, *in vitro* tests are used to initially assess platelet preparations, but licensing of any new platelet product currently requires *in vivo* survival studies in autologous volunteers. The FDA now requires that new candidate platelet products must be directly compared to fresh whole blood–derived platelets in dual radiolabeling experiments. To be licensed, a candidate platelet product will need to demonstrate at least 66% of both the recovery and survival of fresh platelets.

Additive Solutions

In the US, platelets are currently stored in plasma only. Optimized synthetic storage media might help attenuate the platelet storage lesion, thereby facilitating extended storage. Numerous platelet additive solutions have been formulated with this idea in mind. Because additive solutions replace 70-80% of the plasma in the original platelet unit, these formulations are predicted to have additional benefits: reduced allergic and febrile transfusion reactions,[33] decreased transfusion of unwanted antibodies (e.g., ABO, HLA) and increased plasma made available for fractionation.[34] Additive solutions could afford technical benefits for pathogen reduction methods as well (PAS-III, or "Inactisol" was created for the EuroSPRITE pathogen reduction study).

The composition of several platelet additive solutions is shown in **Table 2**. The latest-generation solutions are currently licensed in Europe; these include PAS-IIIM (MacroPharma) and Composol (Fresenius). PlasmaLyte A (Baxter), initially formulated as an intravenous replacement fluid, is the only similar product that is licensed in the US. In an additive solution unit, the final medium contains 20-30% donor plasma. This carried-over plasma provides glucose for platelet metabolism. PAS-IIIM, Composol and PlasmaLyte A also contain acetate, which serves as a second metabolic fuel. Acetate has the added benefit of acting as a buffer. Bicarbonate, the most important physiologic buffer, has been found unsuitable for product manu-

Table 2. Composition of various platelet additive solutions. All values in mmol/L.*

	PlasmaLyte A	PAS-II	PAS-III	PAS-IIIM	Composol
NaCl	90	115.5	77.3	69.3	90
KCl	5	–	–	5	5
$MgCl_2$	3	–	–	1.5	1.5
Na_3 citrate	–	10	10.8	10.8	11
Na phosphate	–	–	28.2	28.2	–
Na acetate	27	30	32.5	32.5	27
Na gluconate	23	–	–	–	23

*Adapted from Ringwald et al.[34]

Downloaded from http://ashpublications.net/hematology/article-pdf/2006/1/492/1091730/492_496ash.pdf by guest on 08 June 2024

facturing and so is no longer included in additive solutions. Magnesium and potassium are present in PAS-IIIM, Composol and PlasmaLyte A. These electrolytes inhibit platelet activation and aggregation, although how they work is unclear.[34] Van der Meer and colleagues[35] compared the *in vitro* storage characteristics of pooled buffy coat platelets stored for up to 12 days in 100% plasma, or in mixtures of plasma with PAS-II, PAS-III, PAS-IIIM and Composol. They observed that several *in vitro* markers of platelet quality (pH ≥ 6.8, glucose consumption, lactate production) were reasonably well preserved for 9-12 days in platelets stored either in 100% plasma, or in PAS-IIIM (30% plasma) or Composol (35% plasma). In general, those additive solution preparations containing higher concentrations of plasma performed better, probably due to the buffering capacity of plasma. As noted above, the value of *in vitro* platelet quality markers is limited. Thus, *in vivo* survival studies of additive solution–stored platelets are now being undertaken.

Refrigerated Storage of Platelets?

Rather than modifying the storage medium to improve and extend platelet storage, another possibility is to modify the platelets themselves. One such strategy, proposed by Hoffmeister and colleagues, is to treat platelets so that they can be stored under refrigeration without a subsequent loss of viability.[36] Platelet refrigeration would significantly reduce the bacterial growth risk, potentially allowing for extended storage. Also, refrigerated platelets could theoretically have functional advantages over room temperature platelets, although this is unproven *in vivo*.[37] When murine platelets are cooled to 4°C for 2 hours, von Willebrand factor receptor (GPIb) complexes cluster together irreversibly on the platelet surface. In this clustered conformation, platelet GPIb molecules are specifically bound by $\alpha_M\beta_2$ integrin receptors on liver macrophages. In turn, the liver macrophages phagocytize the platelets, pulling them out of the circulation.[38] The critical binding interaction involves an $\alpha_M\beta_2$ integrin receptor lectin domain that recognizes β-*N*-acetylglucosamine (β-GlcNAc) residues present on GPIb N-linked oligosaccharides. In mice, it has been possible to inhibit this binding—and thus prevent the clearance of chilled platelets—by coating platelet β-GlcNAc residues with galactose.[36] Whether this strategy can be translated into human platelet products suitable for refrigerated storage remains to be seen.

Platelet Dosing

Apart from extending platelet storage, there exist other strategies to stretch the available supply of platelets. One very successful maneuver was simply lowering the transfusion trigger for prophylactic platelet transfusion from 20,000/μL to 10,000/μL. This change, found to be safe in a number of studies,[39,40] is thought to have reduced the number of platelet doses transfused in the US by 20-30%,[41] although no large-scale studies have been performed to determine the actual impact of the altered transfusion threshold.

A complementary approach to lowering the trigger is altering the dose of prophylactic platelets provided. There are thought to be two separate clearance mechanisms for platelets. Most platelets undergo senescence following a lifespan within the circulation of ~10 days. There is also evidence for a fixed daily loss of platelets that occurs independent of platelet age. Platelets exiting the circulation via this second route (estimated to be 7.1×10^9 platelets/L/day) are postulated to function in maintaining vascular integrity.[42] In principle, a low dose of platelets could be used to fulfill this daily requirement, and mathematical modeling suggests that using a low dose (e.g., pools of 3 whole blood–derived platelets versus the current 6) would save ~22% of prophylactic platelets over time.[43] On the other hand, higher prophylactic platelet doses would be predicted to reduce the total number of transfusion events.[44]

To determine empirically the optimal prophylactic platelet dose, a randomized controlled trial is now being conducted by the Transfusion Medicine/Hemostasis Clinical Trials Network.[45] In this study, termed "PLADO" (platelet dosing), thrombocytopenic patients are randomized to one of three arms: medium (standard) platelet dose (2.2×10^{11} platelets/m^2); low dose (1.1×10^{11} platelets/m^2); or high dose (4.4×10^{11} platelets/m^2). Patients receive prophylactic transfusions for a morning platelet count of ≤ 10,000/mL. The primary end point is the percentage of patients with Grade 2 or higher bleeding in each arm. The plan is to enroll a total of 1350 patients. This study will be completed in 2007 and is expected to have a broad impact on how prophylactic platelets are administered moving forward.

References

1. Stramer SL, Glynn SA, Kleinman SH, et al. Detection of HIV-1 and HCV infections among antibody-negative blood donors by nucleic acid-amplification testing. N Engl J Med. 2004;351:760-768.
2. Busch MP, Kleinman SH, Nemo GJ. Current and emerging infectious risks of blood transfusions. JAMA. 2003;289:959-962.
3. Murphy S, Gardner FH. Effect of storage temperature on maintenance of platelet viability—deleterious effect of refrigerated storage. N Engl J Med. 1969;280:1094-1098.
4. Hillyer CD, Josephson CD, Blajchman MA, Vostal JG, Epstein JS, Goodman JL. Bacterial contamination of blood components: risks, strategies, and regulation: joint ASH and AABB educational session in transfusion medicine. Hematology (Am Soc Hematol Educ Program). 2003:575-589.
5. Brecher ME, AuBouchon J, Yomtovian R, Ness PM, Blajchman MA. Open letter to the Blood Collection Community; August 16, 2002. http://cbbsweb.org/enews/bacterial_risk.pdf
6. Silva M, ed. Standards for Blood Banks and Transfusion Services (ed 24). Bethesda, Maryland: AABB; 2006.
7. Boomgaard MN, Joustra-Dijkhuis AM, Gouwerok CW, et al. In vitro evaluation of platelet concentrates, prepared from pooled buffy coats, stored for 8 days after filtration. Transfusion. 1994;34:311-316.
8. Heddle NM, Cook RJ, Blajchman MA, et al. Assessing the effectiveness of whole blood-derived platelets stored as a pool: a randomized block noninferiority trial. Transfusion.

Downloaded from http://ashpublications.net/hematology/article-pdf/2006/1/492/1091730/492_496ash.pdf by guest on 08 June 2024

2005;45:896-903.
9. Heddle NM, Barty RL, Sigouin CS, et al. In vitro evaluation of prestorage pooled leukoreduced whole blood-derived platelets stored for up to 7 days. Transfusion. 2005;45:904-910.
10. Burstain JM, Brecher ME, Workman K, Foster M, Faber GH, Mair D. Rapid identification of bacterially contaminated platelets using reagent strips: glucose and pH analysis as markers of bacterial metabolism. Transfusion. 1997;37:255-258.
11. Blajchman MA, Goldman M, Baeza F. Improving the bacteriological safety of platelet transfusions. Transfus Med Rev. 2004;18:11-24.
12. Ness P, Braine H, King K, et al. Single-donor platelets reduce the risk of septic platelet transfusion reactions. Transfusion. 2001;41:857-861
13. Perez P, Salmi LR, Follea G, et al. Determinants of transfusion-associated bacterial contamination: results of the French BACTHEM Case-Control Study. Transfusion. 2001;41:862-872.
14. Kuehnert MJ, Roth VR, Haley NR, et al. Transfusion-transmitted bacterial infection in the United States, 1998 through 2000. Transfusion. 2001;41:1493-1499.
15. Fang CT, Chambers LA, Kennedy J, et al. Detection of bacterial contamination in apheresis platelet products: American Red Cross experience, 2004. Transfusion. 2005;45:1845-1852.
16. Holme S, Bunch C, Selman B. Bacterial contamination in stored platelets: performance of the Pall eBDS system under routine use conditions. Vox Sang. 2005;89 (Suppl 1):95.
17. Larsen CP, Ezligini F, Hermansen NO, Kjeldsen-Kragh J. Six years' experience of using the BacT/ALERT system to screen all platelet concentrates, and additional testing of outdated platelet concentrates to estimate the frequency of false-negative results. Vox Sang. 2005;88:93-97.
18. Knutson F, Alfonso R, Dupuis K, et al. Photochemical inactivation of bacteria and HIV in buffy-coat-derived platelet concentrates under conditions that preserve in vitro platelet function. Vox Sang. 2000;78:209-216.
19. Blajchman MA, Beckers EA, Dickmeiss E, Lin L, Moore G, Muylle L. Bacterial detection of platelets: current problems and possible resolutions. Transfus Med Rev. 2005;19:259-272.
20. te Boekhorst PA, Beckers EA, Vos MC, Vermeij H, van Rhenen DJ. Clinical significance of bacteriologic screening in platelet concentrates. Transfusion. 2005;45:514-519.
21. Benjamin RJ, Mintz PD. Bacterial detection and extended platelet storage: the next step forward. Transfusion. 2005;45:1832-1835.
22. Vostal JG. Update on FDA Review of Bacterial Detection Devices for a Platelet Release Test Indication and Extension of Platelet Dating. Washington, D.C.: U.S. Dept. of Health and Human Services; 2005
23. Hall J, Litwak G, Lajoie C, et al. Detection of culture-positive platelet units by testing in-date and out-date platelet concentrates with the platelet PGD® test. Transfusion. 2004;44, Supplement:48A-49A
24. Kirby C I, Inc., Boston, MA. A Rapid Assay For The Detection Of Bacteria In Platelet Units. Transfusion. 2005;45 Suppl:53A-54A
25. Rapid Tests for Detection of Bacterial Contamination of Platelets for Transfusion. Blood Products Advisory Committee. March 9-10, 2006, Gaithersburg, MD
26. Holme S. Storage and quality assessment of platelets. Vox Sang. 1998;74 Suppl 2:207-216.
27. Seghatchian J, Krailadsiri P. The platelet storage lesion. Transfus Med Rev. 1997;11:130-144.
28. Murphy S. What's so bad about old platelets? Transfusion. 2002;42:809-811.
29. AuBuchon JP, Herschel L, Roger J, Murphy S. Preliminary validation of a new standard of efficacy for stored platelets. Transfusion. 2004;44:36-41.
30. Dumont LJ, AuBuchon JP, Whitley P, et al. Seven-day storage of single-donor platelets: recovery and survival in an autologous transfusion study. Transfusion. 2002;42:847-854.
31. Rinder HM, Smith BR. In vitro evaluation of stored platelets: is there hope for predicting posttransfusion platelet survival and function? Transfusion. 2003;43:2-6.
32. Rinder HM, Snyder EL, Tracey JB, et al. Reversibility of severe metabolic stress in stored platelets after in vitro plasma rescue or in vivo transfusion: restoration of secretory function and maintenance of platelet survival. Transfusion. 2003;43:1230-1237.
33. de Wildt-Eggen J, Nauta S, Schrijver JG, van Marwijk Kooy M, Bins M, van Prooijen HC. Reactions and platelet increments after transfusion of platelet concentrates in plasma or an additive solution: a prospective, randomized study. Transfusion. 2000;40:398-403.
34. Ringwald J, Zimmermann R, Eckstein R. The new generation of platelet additive solution for storage at 22 degrees C: development and current experience. Transfus Med Rev. 2006;20:158-164.
35. van der Meer PF, Pietersz RN, Reesink HW. Storage of platelets in additive solution for up to 12 days with maintenance of good in-vitro quality. Transfusion. 2004;44:1204-1211.
36. Hoffmeister KM, Josefsson EC, Isaac NA, Clausen H, Hartwig JH, Stossel TP. Glycosylation restores survival of chilled blood platelets. Science. 2003;301:1531-1534.
37. Kaufman RM. Uncommon cold: could 4 degrees C storage improve platelet function? Transfusion. 2005;45:1407-1412.
38. Hoffmeister KM, Felbinger TW, Falet H, et al. The clearance mechanism of chilled blood platelets. Cell. 2003;112:87-97.
39. Rebulla P, Finazzi G, Marangoni F, et al. The threshold for prophylactic platelet transfusions in adults with acute myeloid leukemia. Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto. N Engl J Med. 1997;337:1870-1875.
40. Wandt H, Frank M, Ehninger G, et al. Safety and cost effectiveness of a 10 x 10(9)/L trigger for prophylactic platelet transfusions compared with the traditional 20 x 10(9)/L trigger: a prospective comparative trial in 105 patients with acute myeloid leukemia. Blood. 1998;91:3601-3606.
41. Slichter SJ. Background, rationale, and design of a clinical trial to assess the effects of platelet dose on bleeding risk in thrombocytopenic patients. J Clin Apher. 2006;21:78-84.
42. Hanson SR, Slichter SJ. Platelet kinetics in patients with bone marrow hypoplasia: evidence for a fixed platelet requirement. Blood. 1985;66:1105-1109.
43. Hersh JK, Hom EG, Brecher ME. Mathematical modeling of platelet survival with implications for optimal transfusion practice in the chronically platelet transfusion-dependent patient. Transfusion. 1998;38:637-644.
44. Norol F, Bierling P, Roudot-Thoraval F, et al. Platelet transfusion: a dose-response study. Blood. 1998;92:1448-1453.
45. Konkle BA, Nemo GJ. Defining effective therapies in transfusion medicine and hemostasis: new opportunities with the TMH Network. Transfusion. 2005;45:1404-1406.

Downloaded from http://ashpublications.net/hematology/article-pdf/2006/1/492/1091730/492_496ash.pdf by guest on 08 June 2024