Indications for platelet transfusion in patients with thrombocytopenia

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Introduction

Stem cell transplantation has become a common therapy in the treatment of a variety of haematological malignancies as well as some non-malignant diseases. Many transplanted patients (up to 83.2%) experience some type of haemostatic complication in the post-transplant period which can range from thrombotic episodes to mild-severe bleeding[1]. Bleeding in these patients is often multifactorial[2], but is strongly associated with prolonged thrombocytopenia and Graft-versus-Host disease (GvHD)[3] and often requires the transfusion of platelet components. This period of thrombocytopenia is typically said to last from 9 to 40 days after transplantation, but can extend from 18 to 240 days in the case of allogeneic transplantation[4] and may be affected by the type of transplant (autologous or allogeneic), source of haematopoietic stem cell product used (bone marrow, peripheral blood stem cells or umbilical cord stem cells), the number of CD34+ cells infused per kilogram of recipient's weight[5], the type of conditioning regimen, the platelet count prior to initiation of therapy, and the severity of GvHD[6]. Even though platelet components are widely available, their transfusion still raises a number of challenges and controversies including the threshold or trigger level for platelet transfusion, the appropriate use of prophylactic and therapeutic platelet transfusions, and the dose of platelets necessary for haemostasis.

This review presents some of the current information available on these and other issues regarding the use of platelet products in thrombocytopenic haematopoietic stem cell transplant recipients.

Prophylactic platelet transfusion

In many hospitals, the majority of platelet transfusions are given to non-bleeding, thrombocytopenic patients to reduce the risk of haemorrhage. In one study, these prophylactic platelet transfusions accounted for as many as 74% of all platelet transfusions[7]. Even though several studies have clearly demonstrated the correlation between thrombocytopenia and the risk of haemorrhage as well as the efficacy of platelet transfusion at reducing that risk, there continues to be controversy regarding the appropriate threshold or "trigger" for prophylactic platelet transfusion -or whether these transfusions are warranted at all.

One of the earliest studies to correlate platelet count with risk of bleeding was that reported by Gaydos *et al.* in which bleeding frequency was compared to platelet count from the records of 92 consecutive, non-transfused, thrombocytopenic patients with acute myeloid leukaemia (AML) or acute lymphocytic leukaemia[8]. The authors found that gross haemorrhage occurred on only 0.8% of days at platelet counts of 20,000/μL to 50,000/μL and on 0.07% of days when the platelet count exceeded 100,000/μL. The authors further stated that "…gross hemorrhage rarely occurred at levels over 20,000/μL…" but that no specific threshold could be established at which platelets should be transfused prophylactically. Nevertheless, partially as a result of this study, it became common practice to use a platelet count of 20,000/μL as the trigger for prophylactic platelet transfusion. However, because the impact of aspirin on platelet function was not appreciated when the study by Gaydos *et al.* was done, and with the more general availability of platelet products for transfusion, there have been a number of more recent studies designed to identify a "trigger" or threshold for prophylactic platelet transfusion. A randomised trial by Heckman *et al.* considered the impact of reducing the platelet transfusion threshold from 20,000/μL to 10,000/μL in 78 adult patients undergoing induction therapy for acute leukaemia[9]. The authors found no statistically significant difference between these groups in morbidity and only a "small adverse effect on bleeding" at the lower threshold. Rebulla *et al.* compared these same platelet transfusion thresholds in 225 patients with newly diagnosed AML[10]. Major bleeding occurred in 21.5% of patients in the group with the 10,000/μL threshold and 20% of patients in the group with the 20,000/μL threshold. Both of these studies suggested, therefore, that there was no clinically significant difference in the frequency of severe bleeding or deaths between patients transfused based on these two platelet transfusion thresholds. While the results of these two randomised, controlled trials strongly suggest that a platelet transfusion threshold of 10,000/μL is safe and effective, Stanworth *et al.* quite appropriately suggested that neither of these studies provided "irrefutable assurance" of this[11]. However, a number of additional prospective trials add support to the efficacy and safety of the lower threshold for platelet transfusion. For example, Navarro *et al.*[12], Lawrence *et*

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al.[13] and Wandt *et al.*[14] also compared the efficacy and safety of a platelet transfusion trigger of 10,000/μL *vs* 20,000/μL and found that bleeding complications were similar in the two groups. Collectively, therefore, these trials certainly support the suggestion that a prophylactic platelet transfusion threshold of 10,000/μL is appropriate and safe for uncomplicated thrombocytopenic patients (for example, those without fever or infection).

In addition to the studies cited above, several investigations have specifically extended the evaluation of prophylactic platelet transfusion thresholds to patients undergoing stem cell transplantation procedures. As early as 1996 Gil-Fernandez *et al.*, in a non-randomised comparison of 190 bone marrow transplant patients, found no difference in bleeding risk when prophylactic platelet transfusions were given at 10,000/μL or 20,000/μL[15]. Similarly, Zumberg *et al.*[16] and Diedrich *et al.*[17] compared these two thresholds for prophylactic platelet transfusion in stem cell transplant patients in randomised trials (including 159 and 166 patients, respectively) and found that bleeding was not increased when the lower threshold was used.

It should be noted here that several studies have evaluated the safety and efficacy of even lower platelet transfusion thresholds. One of these studies was a prospective trial of 81 patients who were randomised to receive platelet transfusions following morning platelet counts of 5,000/μL, 10,000/μL, or 20,000/μL. Red cells were labelled with[51] chromium and stool blood loss was calculated, which did not differ among patients in these three groups, but there was a statistically significant difference in the number of platelet transfusions among the groups[18].

The preceding discussion has largely focused on the prophylactic transfusion of platelets in thrombocytopenic patients to reduce the risk of bleeding in non-bleeding patients. It has been suggested that patients who are expected to undergo invasive procedures may benefit from a somewhat higher platelet count, with 50,000/μL often suggested[19]. Regrettably, there is little evidence to support this recommendation which is based largely on expert opinion in the form of practice guidelines[20] and a limited number of studies. A study by Bishop *et al.* in 95 patients undergoing a variety of invasive procedures demonstrated no excess bleeding when the platelet count exceeded 50,000/μL[21]. Another study by Toy and McVay reviewed the results of 291 consecutive liver biopsies and found the same incidence of bleeding in patients with platelet counts between 50,000/μL and 99,000/μL and patients who had mid-range normal platelet counts; 3.4% in both groups[22]. However, neither of these studies considered the risk of haemorrhage at platelet counts below 50,000/μL. Finally, in a review of 5,609 lumbar punctures, Howard *et al.* noted that there were no indications of haemorrhage even at platelet counts down to 20,000/μL[23].

Therapeutic platelet transfusion

This above discussion focused on the prophylactic transfusion of platelets to reduce the risk of bleeding in thrombocytopenic patients. However, because transfusion carries the risk of adverse reactions and the potential for disease transmission, even though minimal, there continues to be interest in reducing the number of transfusions necessary to support patients' needs. This, plus the fact that platelets are a limited resource and represent a significant cost to the patient and hospital, have stimulated interest in the potential benefit of a therapeutic platelet transfusion protocol and whether this approach might result in the need for fewer platelet transfusions. As long ago as 1992, Patten described the dramatic increase in the transfusion of platelet products in the preceding 25 years and indicated that the majority of these transfusions were given prophylactically[24]. The author went on to suggest that based on his review of the literature at that time "a program of therapeutic platelet transfusion should be considered as a justifiable alternative to prophylactic transfusion in patients with acute leukemia". The author noted that this does not increase mortality or serious bleeding but results in a decrease in platelet use (by as much as 50% in two studies reviewed by the author) and, therefore, both donor exposure and costs. Unfortunately, none of the studies cited was experimentally robust with large numbers of patients. Thus, while a therapeutic platelet transfusion strategy is generally acknowledged to result in fewer platelet transfusion episodes, the question of patients' safety and the risk of serious bleeding have continued to be controversial. In a large retrospective review of 2,942 thrombocytopenic oncology patients over a 10-year period, Friedmann *et al.* also found no relationship between first morning platelet count or the lowest daily platelet count and bleeding using multiple logistic analysis[25]. This prompted the authors to suggest that therapeutic use of platelet products would be more appropriate than prophylactic platelet transfusion based solely on platelet count.

More recently, Wandt *et al*. studied 106 consecutive patients undergoing autologous peripheral blood stem cell transplantation who were transfused with platelets only when bleeding occurred (more than petechial bleeding)[26]. In only 19% of these patients did mild to moderate bleeding require platelet transfusion and no severe or life-threatening bleeding occurred. Wandt *et al.* followed this study with a larger multicentre, open-label, randomised trial comparing prophylactic platelet transfusion using a transfusion trigger of 10,000/μL[27]. The primary end-point of the study was the number of platelet transfusions given during the standardised 14-day observation period. This study enrolled patients undergoing intensive chemotherapy

for AML and patients undergoing autologous stem cell transplantation for haematological cancers. The authors noted that the therapeutic strategy significantly reduced the number of platelet transfusions by over 30% in both the AML patients and the patients undergoing autologous stem cell transplantation. They also reported that the risk of World Health Organisation (WHO) grade II or higher bleeding was greater in the therapeutic group than in the prophylactic group for all patients and was also higher in patients with AML than in patients undergoing autologous stem cell transplantation. Consistent with the previous study by this group, the therapeutic platelet transfusion protocol did not increase the risk of major haemorrhage in patients undergoing autologous stem cell transplantation compared to the risk in patients managed with the prophylactic transfusion protocol. Among these patients there were only rare WHO grade 3 bleeds and no grade 4 bleeds. However, in patients with AML the therapeutic protocol resulted in an increased number of WHO grade 3 bleeds and 17 patients (8.9%) experienced WHO grade 4 haemorrhage. The authors noted that in 15 of the patients who experienced grade 4 haemorrhage the bleeding was adequately controlled by platelet transfusion or local intervention; two patients died, but in both circumstances the authors noted that the established study protocol had been violated. As a result of these findings, the authors suggested that a therapeutic platelet transfusion protocol is safe and effective for clinically stable patients undergoing stem cell transplantation in haematology centres with well-trained and experienced staff. On the other hand, they suggested that routine prophylactic platelet transfusion with a transfusion trigger of 10,000/μL is more appropriate for patients with AML.

In another open-label, non-inferiority trial, Stanworth *et al*. compared a prophylactic platelet transfusion protocol *vs* a therapeutic approach (i.e. no-prophylaxis): patients were randomised to receive prophylactic platelet transfusions when the morning platelet count was 10,000/μL or not to receive these transfusions based on platelet count alone[28]. The patients enrolled in this study were adults (16 years of age or older) who were receiving either induction or consolidation chemotherapy or were undergoing a stem cell transplant procedure which most often was an autologous transplant (70%) although 13% of the patient received an allogeneic transplant. Patients undergoing these various therapeutic modalities were equally distributed between the prophylactic and therapeutic transfusion arms of the study. The objective of this study was to determine whether or not a no-prophylaxis approach to platelet transfusion was as safe as (or non-inferior to) giving platelet transfusions as prophylaxis when the platelet count was less than 10,000/μL. The primary outcome of the trial was the appearance of WHO grade 2, 3, or 4 bleeding within 30 days of randomisation. This end-point occurred in 50% of the no-prophylaxis (therapeutic) group and 43% of the prophylaxis group. Thus, this study did not show that no prophylaxis was non-inferior to prophylaxis. The patients in the no-prophylaxis group had more days of bleeding (rate ratio, 1.52; 95% confidence interval, 1.14 to 2.03; p=0.004) and had a significantly shorter time to first bleed (p=0.02) than patients in the prophylaxis group. The proportion of patients transfused with platelets was lower in the no-prophylaxis group (59%) than in the prophylaxis group (89%). Stanworth *et al.* stated that their results support the continued use of prophylactic platelet transfusions.

While both of these trials provided important information, they are not entirely comparable. For example, the rates of bleeding assessed in the two studies were based on different time-frames (14 days in the study by Wandt *et al.* and 30 days in the trial reported by Stanworth *et al.*); similarly, the grading systems for bleeding differed in that no skin bleeding was included in the grading system used by Wandt *et al.* There were also differences in the study designs and populations. Stanworth *et al.* reported the results of a non-inferiority study based on the clinical appearance of bleeding. Wandt *et al.*, on the other hand, established platelet use as the end-point of their study. Another point of distinction between these two studies is that Wandt *et al.* limited the study population to patients receiving autologous stem cell transplants and to patients undergoing intensive chemotherapy for AML while Stanworth *et al.* also included patient undergoing allogenetic stem cell transplantation.

In spite of these methodological differences, a number of important points can be made. Both studies clearly demonstrated that a therapeutic (or no-prophylaxis) approach to platelet transfusion therapy results in fewer platelet transfusions. Given that transfusion itself carries some risk, albeit perhaps only modest, this should be considered in the safety profile of alternative platelet transfusion protocols. Secondly, both studies demonstrated that a therapeutic transfusion protocol results in increased risks of WHO grade 2, 3, and 4 bleeds among some populations of patients. Finally, both studies suggest that the patients' clinical diagnosis may influence risk of bleeding. In the study by Wandt *et al.* patients with AML had a significantly ($p<0.0001$) higher risk of bleeding than patients undergoing an autologous stem cell transplant and grade 4 bleeding occurred only among the patients being treated for AML. In the study by Stanworth *et al.*, there was an indication that the effectiveness of prophylactic platelet transfusions may vary depending on the patients' clinical diagnosis. In order to investigate this further, Stanworth *et al.* performed a subgroup analysis[29] of the data derived from their trial. In this subgroup analysis there was a reduction

in the proportion of patients experiencing WHO grade 2, 3, and 4 bleeds in the prophylaxis arm of the trial but this reduction was of much greater magnitude in patients treated with chemotherapy and allogeneic transplantation than among patients undergoing an autologous stem cell transplant procedure.

Platelet dose

Given that platelet transfusion, whether prophylactic or therapeutic, will reduce the risk of thrombocytopenia-related bleeding, the "dose" of platelets that is effective has been somewhat arbitrarily set at a single apheresis platelet product containing a minimum of 3.0×10^{11} platelets or four to six whole blood-derived platelet concentrates, each of which must have a minimum of 5.5×10^{10} platelets. The appropriate "dose" of platelets has recently been more carefully assessed in two randomised controlled trials. The PLADO trial was a multicentre, randomised controlled trial (RCT) that enrolled 1351 patients and compared three different doses of platelets with the risk of WHO grade 2 bleeding[30]. The three doses were 1.1×10^{11} platelets/m^2, 2.2×10^{11} platelets/m^2, and 4.4×10^{11} platelets/m^2. Platelets were transfused when the morning platelet count was 10,000/μL or less. The study demonstrated that while the incidences of higher grades of bleeding and other adverse effects were similar among all three groups, the number of platelet transfusions given was significantly higher in the low-dose group than in the medium-dose and high-dose groups. The second trial, the Strategies for Platelet Transfusion or SToP trial, another multicentre, randomised controlled trial, evaluated a low-dose platelet transfusion ($1.5\text{-}2.9\times10^{11}$platelets/product) to a high-dose transfusion ($3.0\text{-}6.0\times10^{11}$) in patients with chemotherapy-induced thrombocytopenia[31]. Patients were transfused at a platelet count of 10,000/μL. This trial was specifically designed to compare platelet transfusion dose with the risk of bleeding. Even though the numbers of patients reaching the end-point of WHO grade 2 or higher bleeding was comparable in the two arms of this study, the trial was stopped early when 5% of the patients in the low-dose arm had grade 4 bleeding. Several older studies, including those by Norol *et al.*[32], Klumpp *et al.*[33] and Sensebe *et al.*[34] also compared the efficacy of a high-dose or low-dose strategy for platelet transfusion. In general, these studies also showed that higher doses result in higher post-transfusion platelet increments and longer intervals between transfusions.

Other considerations in platelet transfusion

This review has thus far focused on haemorrhagic risk in thrombocytopenic patients based on platelet count alone; however, several other factors may influence the risk of bleeding in thrombocytopenic patients.

Minor bleeding predictive of more severe bleeding

In a study of bleeding risks in thrombocytopenic patients, Webert *et al.* noted that the majority of severe bleeds were preceded by bleeds of lesser severity[35]. Even patients with petechiae (WHO grade 1 bleeding) were 2.5 times more likely to experience clinically significant bleeding on the next day; patients experiencing WHO grade 1 or 2 bleeding were three times more likely to have a severe bleed the next day. In a large retrospective study including 2,942 patients, Friedmann *et al.* demonstrated a highly significant association between the risk of haemorrhage and a previous bleed[25]. It is also worth noting that in their multivariate analysis, other factors significantly associated with an increased risk of bleeding in thrombocytopenic patients included uraemia, hypoalbuminaemia, and a recent bone marrow transplant.

Body temperature and bleeding

Slichter *et al.* demonstrated that the presence of fever was significantly associated with an increased risk of refractoriness to platelet transfusions[36]. Goldberg *et al.* showed that there was a poorer platelet increment following transfusion in the presence of fever, but they were unable to demonstrate that fever or bacteraemia was associated with an increased risk of bleeding[37]. However, in the article cited above, Webert *et al.* were the first to document that an elevated body temperature or a clinical diagnosis of infection on the previous day were both associated with an increased risk of all grades of bleeding[35]. The presence of clinical infection was a statistically significant predictor of bleeding with the risk of grades 2, 3, or 4 bleeding increasing 3.35 times.

Haemoglobin concentration and bleeding

Valeri *et al.* reported that patients' haematocrit may play a role in the risk of bleeding in thrombocytopenic patients[38]. They noted that in normal volunteers when the platelet count was reduced by apheresis procedures, but the haematocrit was unaffected, there was no significant change in bleeding time. On the other hand when both red cells and platelets were removed (haematocrit reduced from 41% to 35%) the bleeding time was almost doubled. It has been suggested that the effect of red blood cells on coagulation might be due to the fact that red cells displace platelets towards the endothelial surface where they can more effectively respond to injury[39,40]. Alternatively, other workers have emphasised the role of red cells in activating the release of ADP from platelets and in stimulating the production of thromboxane A_2[41]. From a practical perspective, this suggests that maintaining haematocrit levels in thrombocytopenic patients might reduce the risk of bleeding. Webert *et al.*

found that higher haemoglobin levels were associated with a delay in the time of the first clinically significant bleed (grades 2-4)[35].

Summary

Platelet transfusion has become a progressively more common and important therapeutic procedure in managing thrombocytopenic patients. Nevertheless, this therapy continues to evolve. Most platelet products are transfused into non-bleeding thrombocytopenic patients. The transfusion "trigger" or threshold for transfusion of these patients is now generally accepted to be 10,000/μL based on the results of a number of studies. However, it is important to emphasise that this "trigger" value generally applies to uncomplicated patients or those who are not febrile, have no infection, or are not being treated with a drug known to damage platelets. Importantly, even with a platelet "trigger" level established at 10,000/μL, platelet transfusion therapy must be individualised to the patient and the clinical situation. As noted above, fever and infection may be correlated with a greater risk of bleeding, but in addition, minor episodes of bleeding may also increase the subsequent risk of clinically significant bleeding; even haemoglobin concentration may play a role in determining bleeding risk. Finally, although prophylactic platelet transfusion is commonly used in the care of thrombocytopenic patients, therapeutic platelet transfusion may represent a reasonable option in managing the bleeding risk of some thrombocytopenic patients. Certainly in the studies by Wandt *et al.*[26,27] and Stanworth *et al.*[28] the use of therapeutic platelet transfusion resulted in an increased bleeding risk. However, in certain populations of patients, the bleeding seen in the therapeutic transfusion programme is generally mild (WHO bleeding category 2 or less). Nevertheless, the studies have repeatedly highlighted the importance of tailoring platelet transfusions to the clinical needs of each patient. While clinical guidelines for platelet transfusion therapy are reasonably well established, a review of the literature clearly indicates that platelet transfusions must be guided by the population of patients under consideration, the clinical conditions of the patients, and perhaps even the resources of the transfusing facility and its ability to respond rapidly to patients' transfusion needs.

Keywords: platelet transfusion, transfusion indications, prophylactic platelet transfusion, therapeutic platelet transfusion, bleeding risk.

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References

1) Nevo S, Enger C, Hartley E, et al. Acute bleeding in thrombocytopenia after bone marrow transplantation. Bone Marrow Transplant 2001; **27**: 65-72.
2) Gajewski JL, Johnson VV, Sandler SG, et al. A review of transfusion practice before, during and after hematopoietic progenitor cell transplantation. Blood 2008; **112**: 3036-47.
3) Pihusch R, Salat C, Schmidt E, et al. Hemostatic complications in bone marrow transplantation: a retrospective analysis of 447 patients. Transplantation 2002; **74**: 1303-9.
4) Davies SM, Kollman C, Anasetti C. Engraftment and survival after unrelated bone marrow transplantation: a report from the National Marrow Donor Program. Blood 2000; **96**: 4096-102.
5) Benn H, Rowley SD. Bone marrow and peripheral blood stem cell transplantation. In: Hillyer CD, Silberstein LE, Ness PM, et al, editors. *Blood Banking and Transfusion Medicine. Basic Principles and Practice.* Philadelphia: Churchill Livingstone Elsevier; 2007. p. 787-822.
6) Prebet T, Ladaique P, Ferrando M, et al. Platelet recovery and transfusion needs after reduced intensity conditioning allogeneic peripheral blood stem cell transplantation. Exp Hematol 2010; **38**: 55-60.
7) Greeno E, McCullough J, Weisdorf D. Platelet utilization and the transfusion trigger: a prospective analysis. Transfusion 2007; **47**: 201-5.
8) Gaydos LA, Freireich EJ, Mantel N. The quantitative relationship between platelet count and hemorrhage in patients with acute leukemia. N Engl J Med 1962; **266**: 905-9.
9) Heckman KD, Weiner GJ, Strauss RG, et al. Randomized study of prophylactic platelet transfusion threshold during induction therapy for adult acute leukemia: 10,000/microL versus 20,000/microL. J Clin Oncol 1997; **15**: 1143-9.
10) Rebulla P, Finazzi G, Marangoni F, et al. The threshold for prophylactic platelet transfusion in adults with acute myeloid leukemia. N Engl J Med 1997; **337**: 1870-5.
11) Stanworth SJ, Hyde C, Brunskill S, Murphy MF. Platelet transfusion prophylaxis for patients with haematological malignancies: where to now? Br J Haematol 2005; **131**: 588-95.
12) Navarro JT, Hernandez JA, Ribera JM, et al. Prophylactic platelet transfusion threshold during therapy for adult acute myeloid leukemia: 10,000/μL versus 20,000/μL. Haematologica 1998; **83**: 998-1000.
13) Lawrence JB, Yomtovian RA, Hammons T, et al. Lowering the prophylactic platelet transfusion threshold: a prospective analysis. Leuk Lymphoma 2001; **41**: 67-76.
14) 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**: 3601-6.
15) Gil-Fernandez JJ, Alegre A, Fernandex-Villalta MJ. Clinical results of a stringent policy on prophylactic platelet transfusion: non-randomized comparative analysis in 190 bone marrow transplant patients from a single institution. Bone Marrow Transplant 1996; **18**: 931-5.
16) Zumberg M, Rosario ML, Nejame CF, et al. A prospective randomized trial of prophylactic platelet transfusion and bleeding incidence in hematopoietic stem cell transplant recipients: 10,000/μL versus 20,000/μL. Biol Blood Marrow Transplant 2002; **8**: 569-76.
17) Diedrich B, Remberger M, Shanwell A, et al. A prospective randomized trial of a prophylactic platelet transfusion trigger of 10 x 10^9 per L versus 30 x 10^9 per L in allogeneic hematopoietic progenitor cell transplant recipients. Transfusion 2005; **45**: 1064-72.
18) Slichter SJ, LeBlanc R, Jones MK. Quantitative analysis of bleeding risk in cancer patients prophylactically transfused at platelet counts of 5,000, 10,000, or 20,000 platelets/μL. Blood 1999; **94**: 376a.
19) Wall MH, Prielipp RC. Transfusion in the operating room and the intensive care unit: current practice and future directions. Int Anesthesiol Clin 2000; **38**: 149-69.

20) British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of platelet transfusions. 2002.
21) Bishop JF, Schiffer CA, Aisner J, et al. Surgery in acute leukemia: a review of 167 operations in thrombocytopenic patients. Am J Hematol 1987; **26**: 147-55.
22) McVay PA, Toy PT. Lack of increased bleeding after paracentesis and thoracentesis in patients with mild coagulation abnormalities. Transfusion 1991; **31**: 164-71.
23) Howard SC, Gajjar AJ, Cheng C, et al. Risk factors for traumatic and bloody lumbar puncture in children with acute lymphoblastic leukemia. JAMA 2002; **288**: 2001-7.
24) Patten E. Controversies in transfusion medicine. Prophylactic platelet transfusion revisited after 25 years: con. Transfusion 1992; **32**: 381-5.
25) Freidmann AM, Sengul H, Lehman H, et al. Do basic laboratory tests or clinical observations predict bleeding in thrombocytopenic oncology patients? A reevaluation of prophylactic platelet transfusions. Transfus Med Rev 2002; **16**: 34-45.
26) Wandt H, Schaefer-Eckart K, Frank M, et al. A therapeutic platelet transfusion strategy is safe and feasible in patients after autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 2006; **37**: 387-92.
27) Wandt H, Schaefer-Eckart K, Wendelin K, et al. Therapeutic platelet transfusion versus prophylactic transfusion in patients with haematological malignancies: an open-label, multicenter, randomized study. Lancet 2012; **380**: 1309-16.
28) Stanworth SJ, Estcourt LJ, Powter G, et al. A no-prophylaxis platelet-transfusion strategy for hematologic cancers. N Engl J Med 2013; **368**: 1771-80.
29) Stanworth SJ, Estcourt LJ, Llewelyn CA, et al. Impact of prophylactic platelet transfusions on bleeding events in patients with hematologic malignancies: a subgroup analysis of a randomized trial. Transfusion 2014; **54**: 2385-93.
30) Slichter SJ, Kaufman RM, Assmann SF, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. N Engl J Med 2010; **362**: 600-13.
31) Heddle NM, Cook RJ, Tinmouth A, et al. A randomized controlled trial comparing standard- and low-dose strategies for transfusion of platelets (SToP) to patients with thrombocytopenia. Blood 2009; **113**: 1564-73.
32) Norol F, Bierling P, Roudot-Thoravel F, et al. Platelet transfusion: a dose-response study. Blood 1998; **92**: 1448-53.
33) Klumpp TR, Herman JH, Gaughan JP, et al. Clinical consequences of alterations in platelet transfusion dose: a prospective, randomized, double-blind trial. Transfusion 1999; **39**: 674-81.
34) Sensebe L, Giraudeau B, Deconinck E, et al. The efficiency of transfusing high doses of platelets in hematologic patients with thrombocytopenia: results of a prospective, randomized, open, blinded end-point (PROBE) study. Blood 2005; **105**: 862-4.
35) Webert K, Cook RJ, Sigouin CS, et al. The risk of bleeding in thrombocytopenic patients with acute myeloid leukemia. Haematologica 2006; **91**: 1530-7.
36) Slichter SJ, Davis K, Enright H, et al. Factors affecting post transfusion platelet increments, platelet refractoriness, and platelet transfusion intervals in thrombocytopenic patients. Blood 2005; **105**: 4106-14.
37) Goldberg GL, Gibbon DG, Smith HO, et al. Clinical impact of chemotherapy-induced thrombocytopenia in patients with gynecologic cancer. J Clin Oncol 1994; **12**: 2317-20.
38) Valeri CR, Cassidy G, Pivacek LE, et al. Anemia-induced increase in the bleeding time: implications for treatment of nonsurgical blood loss. Transfusion 2001; **41**: 977-83.
39) Turitto VT, Weiss HJ. Red blood cells: their dual role in thrombosis formation. Science 1980; **207**: 541-3.
40) Uijttewaal WS, Nijhof EJ, Bronkhorst PJ, et al. Near-wall excess of platelets induced by lateral migration of erythrocytes in flowing blood. Am J Physiol 1993; **264**: H1239-44.
41) Valles J, Santos MT, Aznar J, et al. Erythrocytes metabolically enhance collagen-induced platelet responsiveness via increased thromboxane production, adenosine diphosphate release, and recruitment. Blood 1991; **78**: 154-62.

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