

## The argument(s) for lowering the US minimum required content of apheresis platelet components

Richard J. Benjamin,<sup>1</sup> Louis Katz,<sup>2</sup> Richard R. Gammon,<sup>3</sup> Susan L. Stramer,<sup>4</sup> and Eva Quinley,<sup>5</sup>  
For the Consortium for Blood Availability

The Platelet Dose (PLADO) study demonstrated that in hospitalized hematology/oncology patients, the use of low platelet doses ( $1.1 \times 10^{11}/\text{m}^2$  body surface area [BSA], equivalent to about  $2.1 \times 10^{11}/\text{bag}$  for a 70 kg patient) that were generally lower than the minimum US content requirement for apheresis platelets ( $\geq 3.0 \times 10^{11}/\text{unit}$ ) led to lower per-patient total number of platelets transfused than with higher doses. There was no impact on patient safety or on clinically significant bleeding. Twofold ( $2.2 \times 10^{11}/\text{m}^2$ ) and fourfold ( $4.4 \times 10^{11}/\text{m}^2$ ) higher doses increased the posttransfusion platelet count increments, decreased the number of platelet components (PCs) transfused, and prolonged the intertransfusion intervals, at the cost of consumption of a higher total number of transfused platelets per patient.<sup>1</sup> Based on these data, some institutions now routinely provide one-half or variable low-platelet content units to selected patient groups.<sup>2</sup> Furthermore, the US Food and Drug Administration (FDA) has licensed blood centers to ship variable-content conventional and pathogen-reduced platelets with platelet counts lower than  $3.0 \times 10^{11}$  for interstate commerce.

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**ABBREVIATIONS:** BSA = body surface area; FDA = Food and Drug Administration; PAS = platelet additive solution; PCs = platelet components; WB = whole blood.

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From the <sup>1</sup>Cerus Corporation, Concord, CA; <sup>2</sup>Americas Blood Centers, Washington, DC; <sup>3</sup>OneBlood, Orlando, Florida; <sup>4</sup>American Red Cross, Gaithersburg, MD; and the <sup>5</sup>Vitalent, Chicago, Illinois.

Address reprint requests to: Richard J. Benjamin, MD, PhD, FRCPath, Cerus Corporation, 2550 Stanwell Drive, Concord, CA 94596; e-mail: rbenjamin@cerus.com

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The current minimum apheresis PC content of  $3.0 \times 10^{11}/\text{unit}$  or more required by the FDA for quality control purposes is empirically derived based on historical manufacturing standards and is not required for pooled whole blood (WB)-derived PCs. The United States should consider the advantages of reducing its apheresis PC minimum content standard to align with international practice ( $\geq 2.5 \times 10^{11}$  platelets, an approx. 17% decrease from the US standard), to increase the number of units in inventories and/or reduce the pressure on blood donors, and to meet current demands that may exceed the available supply. This change would also help to compensate for the increased processing losses necessary to implement bacterial risk mitigation strategies such as large volume cultures and pathogen reduction technology. Simultaneously, a requirement to label every PC with the actual platelet content would allow clinicians to more accurately correlate and predict clinical outcomes with the platelet dose transfused.

### BACKGROUND

During the past decade, patient blood management has revolutionized the practice of RBC transfusion, as multiple randomized controlled studies have demonstrated the safety of defined and generally lower transfusion thresholds in a variety of medical and surgical clinical settings.<sup>3</sup> RBC use has declined by approximately 25% to 30% in the United States, without measured adverse effects on patient outcomes and with reduced costs.<sup>4</sup> During the same period, the practice of PC transfusion has changed very little: Minimum prophylactic platelet count transfusion thresholds are well defined in nonbleeding, hospitalized, thrombocytopenic hematology/oncology patients, but these account for less than one-half of PC transfusions.<sup>5</sup> Use is more variable in the outpatient and surgical settings.<sup>6</sup> Here, the triggers for transfusion and recommendations for dosing are weakly evidence-based, and platelets are usually administered by the “bag” after reaching a threshold trigger, without physician knowledge of the number of platelets transfused or accounting for patient size or measurement of corrected count increment to assess clinical impact.<sup>7</sup>

The *Circular of Information*, recognized as acceptable by the FDA,<sup>8</sup> states that

the number of platelet units to be administered depends on the clinical situation of each patient. One unit of platelets would be expected to increase the platelet count of a 70-kg adult by 5,000 to 10,000/ $\mu\text{L}$  and increase the count of an 18-kg child by 20,000/ $\mu\text{L}$ . The therapeutic adult dose is 1 unit of Apheresis Platelets or 4 to 6 units of whole blood (WB)-derived platelets, either of which usually contain  $\geq 3.0 \times 10^{11}$  platelets.<sup>8</sup>

Within these imprecise guidelines that are linked to count increments and not to the risk of bleeding, overall PC consumption in the United States has remained relatively stable and few clinical trials have addressed optimal use in non-hematology/oncology patients.<sup>9</sup>

The short (5–7 days) shelf life of PCs results in irregular, often local or regional, shortages as hospital demand fluctuates based on individual patient needs and the supply varies subject to vagaries of donor availability, for example, weather and holidays. Shortages could be exacerbated by recent changes in the donor suitability requirements, for example, the increase in the minimum hemoglobin requirement for men (from 12.5 g/dL to 13.0 g/dL) and the implementation of transfusion-related acute lung injury mitigation strategies that led to the deferral of up to 20% of previously acceptable female donors.<sup>10</sup>

There is an opportunity to change platelet transfusion practice in the United States and possibly to address shortages and improve patient outcomes by optimizing PC content, platelet dosing strategies, and transfusion thresholds, in concert with improved inventory management and extension of shelf life to 7 days.

### Current US platelet dose strategies

Approximately 2 million PCs are transfused each year in the United States to treat (therapeutic) or prevent (prophylactic) bleeding.<sup>9</sup> In a recent National Heart, Lung, and Blood Institute-funded survey, 84% of PCs were transfused to inpatients and 16% to outpatients, mostly for bleeding prophylaxis.<sup>11</sup> The United States has among the highest PC per capita use in the world (Fig. 1: approx. 7.0 PCs per 1000 population/year).<sup>12</sup> The US minimum apheresis PC content of  $3.0 \times 10^{11}$  or more<sup>13</sup> is also higher than in most other countries, with the European Directorate for the Quality of Medicines standard being greater than  $2.0 \times 10^{11}$  and most countries requiring at least  $2.0$  to  $2.5 \times 10^{11}$  platelets per unit (Table 1). Lower PC content does not generally correlate with more platelet transfusions on a national scale, as per capita PC use and minimum PC content do not appear to be inversely correlated (Table 1): For example, Belgium has a minimum requirement similar to that of the United States of  $3.0 \times 10^{11}$  or more, and has a similar high per capita platelet use (6.2/1000; Table 1), while France and Switzerland have lower minimum required pathogen-reduced platelet content ( $2.0 \times 10^{11}$  and  $2.4 \times 10^{11}$ , respectively) and lower per capita use (4.8/1000 and 4.3/1000,

respectively). The combination of high per capita use and high content in the United States requires frequent collection of large numbers of platelets from each donor, causing a strain on the supply chain and exacerbating the risk of shortages.

In contemporary US practice, pooled WB platelets are only 5% to 10% of all platelet transfusions. Pool sizes vary from 4 to 6 WB platelet concentrates with 75% of concentrates tested required to contain  $5.5 \times 10^{10}$  or more platelets. The minimum requirement for pooled WB platelets varies according to the number of individual concentrates pooled, as individual centers titrate the pool size to give an average content similar to apheresis PCs (Table 1).<sup>8</sup> The minimum requirement for apheresis PCs of  $3.0 \times 10^{11}$  or more platelets per unit (equivalent to a pool of approx. 5.5 WB platelets) was derived empirically more than 30 years ago. The requirement was not drawn from data on efficacy in preventing or treating bleeding; rather, it was based on the ability to generate a single dose of platelets by apheresis roughly equivalent to a WB platelet “six-pack.”<sup>14,15</sup> Studies showed that higher platelet doses gave larger count increments in patients with high BSA or total blood volume and could extend the intertransfusion interval.<sup>16</sup> In practice, the actual platelet content is not generally recorded on the container by most blood centers, and physicians do not know the dose they are transfusing unless they estimate from the pool size and quality control requirements. This prevents physicians from tailoring treatment to an individual adult patient based on clinical need, patient weight, blood volume, or measured corrected count increment. The exception is dosing by patient weight that is the norm for pediatric patients.

In the past 15 years, blood centers have increasingly split high-content apheresis collections into two or three individual units, each containing a minimum of  $3.0 \times 10^{11}$  or more platelets. Today, more than 90% of PC transfusions in the United States are from apheresis collections, and most are derived from split collections.<sup>9</sup> The overall effect has been a lowering of the average apheresis PC content toward the minimum required content of  $3.0 \times 10^{11}$  or more. For the most part, few higher-content apheresis PCs are distributed to hospitals, and physicians are generally unable to request high-content PCs for their patients. Pools of six WB platelets also historically contained far in excess of approximately  $3.0 \times 10^{11}$  platelets, but now have progressively contained lower contents where fewer WB concentrates are included in pools. An unanswered question is whether the  $3.0 \times 10^{11}$  or more criterion is the appropriate dose for all patients and whether certain clinical situations may require smaller (e.g., partial units, as used in pediatrics) or larger (multiple units) doses, according to the clinical setting?

### The US should consider a lower minimum content ( $\geq 2.5 \times 10^{11}$ ) of apheresis platelets and use multiple-unit PC transfusions where indicated

With the empirical nature of the current standard, the United States should consider the potential advantages of reducing its minimum platelet content standard to  $2.5 \times$

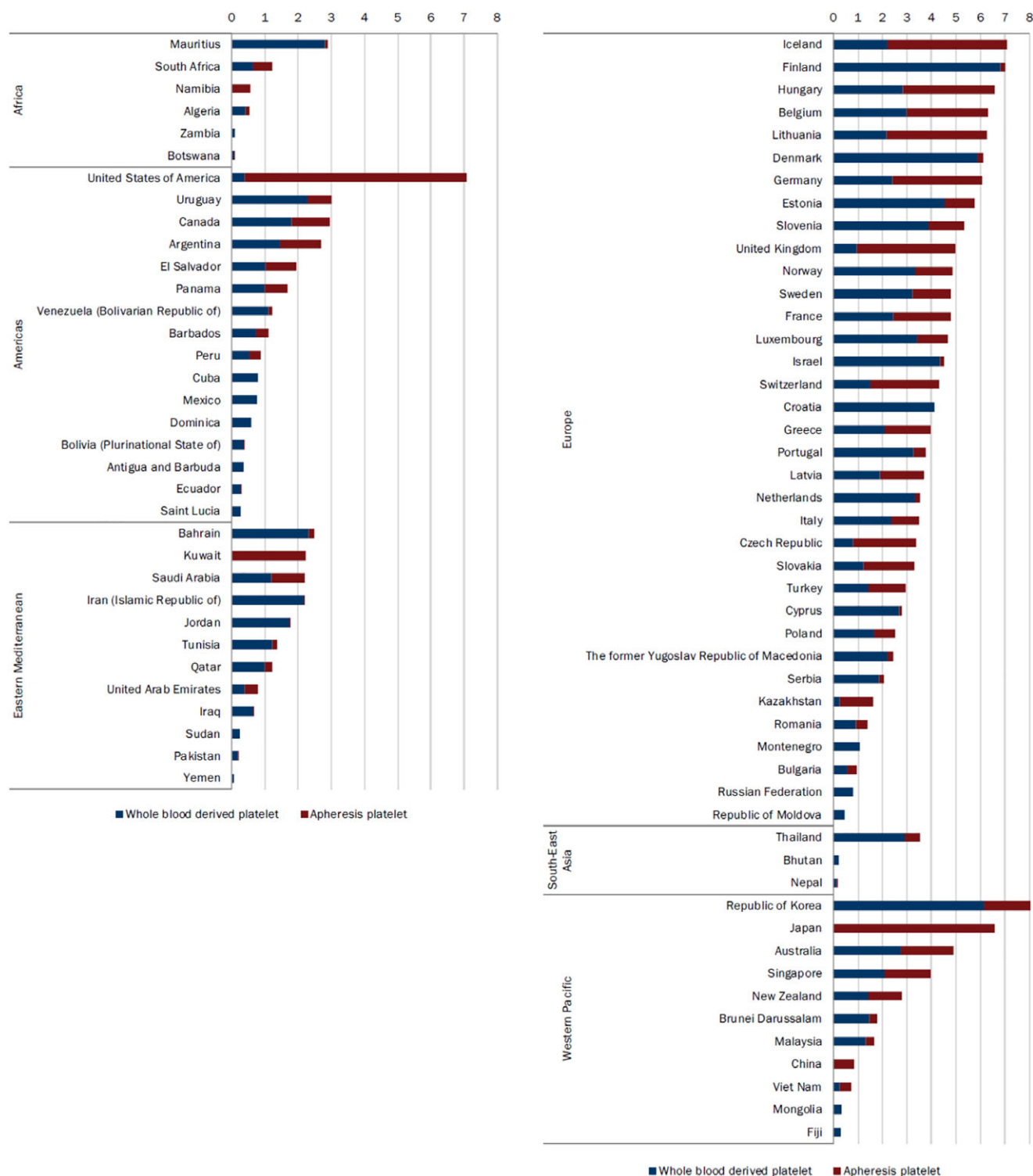


Fig. 1. Units of PCs transfused per 1000 population in countries segregated by World Health Organization region. Reprinted from the "Global Status Report on Blood Safety and Availability 2016." Geneva: World Health Organization; 2017. Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO license: CC BY-NC-SA 3.0 IGO. [Color figure can be viewed at wileyonlinelibrary.com]

10<sup>11</sup> or more, to align with international practice. The PLADO study demonstrated that 1.1 × 10<sup>11</sup> platelets/m<sup>2</sup> BSA (equivalent to a median dose of 2.1 × 10<sup>11</sup> platelets

given to a 70-kg subject) led to a lower overall total number of platelets used.<sup>1</sup> Where indicated, higher doses can be achieved by using multiple-unit transfusions where there is

**TABLE 1. International platelet use per capita and minimum platelet content requirements**

Country	Platelet use per 1000 population*	Platelet type	Minimum required dose ( $\times 10^{11}$ )	Actual mean content ( $\times 10^{11}$ )	Ref.
United States	7.1	Apheresis	3.0		13
		Four pooled WB <sup>†</sup>	2.2		8
		Five pooled WB <sup>†</sup>	2.75		
		Six pooled WB <sup>†</sup>	3.3		
Canada	2.9	Apheresis	2.4	3.7	40
		Pooled WB <sup>§</sup>	2.4	3.0	
Australia	4.9	Apheresis	2.0	2.8	41
		Pooled WB <sup>§</sup>	2.4	2.8	42
Europe (EDQM)		Apheresis and pooled WB	2.0		43
United Kingdom	5.0	Apheresis and pooled WB <sup>§</sup>	2.4		44
Netherlands	3.5	Apheresis and Pooled WB <sup>§</sup>	2.5		45
France <sup>‡</sup>	4.8	Pathogen reduced, apheresis, and pooled WB <sup>§</sup>	2.0	Variable	16,46
Switzerland <sup>‡</sup>	4.3	Pathogen reduced, apheresis, and pooled WB <sup>§</sup>	2.4		47
Belgium <sup>‡</sup>	6.2	Pathogen reduced, apheresis, and pooled WB <sup>§</sup>	3.0		48
Germany	6.0	Apheresis and pooled WB <sup>§</sup>	2.0		49
		Pathogen reduced, apheresis, and pooled WB <sup>§</sup>	2.5		
South Africa	1.3	Apheresis and pooled WB <sup>§</sup>	2.4		50

\* Data from the World Health Organization, 2016.<sup>12</sup>

† WB-derived platelets prepared with the platelet-rich plasma method in plasma or PAS.

‡ Implemented universal pathogen reduction with the amotosalen/ultraviolet A method (INTERCEPT, Cerus Corp).

§ BC = pooled, buffy coat platelets derived from WB donations in plasma or PAS.

EDQM = European Directorate for the Quality of Medicines; PAS = platelet additive solution; WB = whole blood.

proven clinical or financial benefit. For example, many PCs are transfused in the outpatient setting as prophylaxis to prevent bleeding. While multiple-unit transfusions in this setting would increase donor exposures and costs (in terms of acquisition cost and increased infusion time), that may be offset by longer intertransfusion intervals and reduced outpatient clinic visits, resulting in lower total infusion cost. Patients would benefit by the reduced inconvenience of frequent outpatient clinic visits and the net cost to the hospital could decline with fewer infusion visits. In the inpatient setting, infusion cost, not acquisition, is the major expense of PC transfusion, and this is likely also the case in the outpatient setting.<sup>17</sup> PC acquisition costs in the outpatient setting (in contrast to inpatient transfusions) are directly reimbursed by payors such as the Centers for Medicare and Medicaid Services. Accordingly, hospitals and blood centers would receive increased revenue per visit from payors when transfusing multiple platelet products, although the number of visits may decline. An appropriate health economic analysis is lacking to determine whether the cost of two PC transfusions resulting in fewer outpatient visits can be justified to the payors in terms of lower overall health care costs. A decision to lower the minimum required platelet content should include a thorough analysis of costs on both the inpatient and outpatient sides, including platelet acquisition, blood

bank, nursing, and infusion cost. One published analysis investigated the overall program costs for low-, medium-, or high-dose platelets as used in the PLADO study for hematology/oncology inpatients, and estimated a cost savings to the hospital for patients receiving the low-dose PCs. This analysis, however, relied heavily on lower acquisition cost from the blood center suppliers for lower doses,<sup>18</sup> and the content differentials (one-half vs. single vs. double doses) were larger than we are proposing.<sup>19</sup> We do not assume that blood collectors would automatically lower the cost of lower-content PCs to hospitals; however, a platelet surplus might cause downward price pressure on the overall PC supply in favor of the hospitals, as has happened with RBCs.

Lowering the US minimum content from  $3.0 \times 10^{11}$  or more to  $2.5 \times 10^{11}$  or more could have favorable potential impacts on patients, blood donors, blood centers, and payors. These may be summarized as follows:

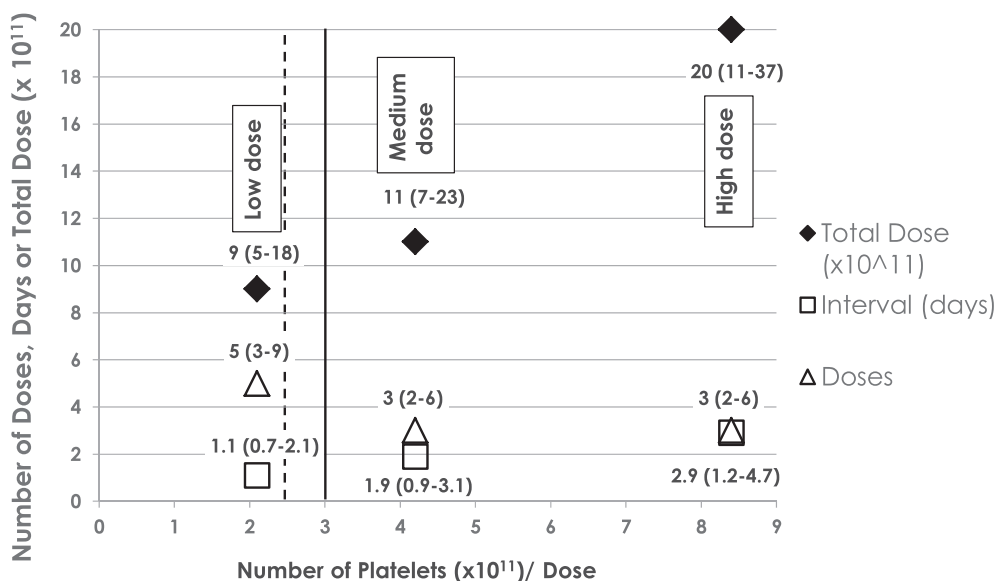
- Increased PC availability due to greater collection split rates, if blood centers chose to maintain current number of platelets collected per donation.
- Retained platelet transfusion efficacy, with increased convenience to patients in the outpatient setting if high doses (e.g., multiple units) are transfused with greater intertransfusion intervals.

**TABLE 2. Analysis of platelet collection split rates using retrospective data at two US blood centers utilizing either the TRIMA EXCEL (Terumo BCT) or Amicus (Fenwal) apheresis separators**

Separator	TerumoBCT TRIMA EXCEL		Fenwal AMICUS	
	Current splits ( $\geq 3.0 \times 10^{11}/\text{unit}$ )	Calculated splits* ( $\geq 2.5 \times 10^{11}/\text{unit}$ )	Current splits ( $\geq 3.0 \times 10^{11}/\text{unit}$ )	Calculated splits ( $\geq 2.5 \times 10^{11}/\text{unit}$ )
Donations (n)		2649		3156
Split components (n)	4432	5376	6324	7762
Split rate	1.67	2.0	2.0	2.3
Component increase	NA	21%	NA	23%

\* Calculated split rate using a yield of  $5.5 \times 10^{11}$ ,  $8.0 \times 10^{11}$  and  $10.5 \times 10^{11}$  as the minimum requirement to split into double, triple, or quadruple units respectively.

NA = not applicable; PC = platelet component.



**Fig. 2. Effect of transfused PC dose on total platelets transfused (diamonds); median number of total doses (triangles); and median intertransfusion interval (squares) for a 70-kg patient with a 1.9-m<sup>2</sup> BSA receiving the low-, medium-, or high-dose regimen in the PLADO study.<sup>1</sup> The solid vertical line represents the current US minimum apheresis PC content requirement; the dashed vertical line represents the proposed minimum standard of  $2.5 \times 10^{11}$ . Numerical results are shown as reported in the PLADO study as median (interquartile range).<sup>1</sup>**

- Possible increased donor safety and convenience if blood centers chose to collect fewer platelets per donation.
- Possible reduced apheresis platelet bacterial contamination.
- Possible economic advantage for hospitals, blood centers, and payors.
- Compensation for increased platelet processing losses likely to occur with pending bacterial risk mitigation strategies such as large volume cultures and pathogen reduction technology.

**Impact on blood centers**

One possible outcome of a reduction in the minimum platelet content would be to allow blood centers to increase the number of PCs derived from each collection by increasing the split rate. Analysis of two large blood center databases, using the yield of  $5.5 \times 10^{11}$ ,  $8.0 \times 10^{11}$ ,

and  $10.5 \times 10^{11}$  as the minimum requirement to split into double, triple, or quadruple units, respectively, reveals an opportunity for a 21% to 23% increase in PCs, if no changes were made to the collection procedures (Table 2). This approach would increase platelet availability without increasing the number of donors or donation events.

**Impact on donors**

An alternative strategy for the blood centers would be to reduce the number of platelets collected from selected, if not all, donors and to maintain the current split rates using shorter times for collection, with less donor discomfort and the possibility of increased donor retention. This strategy would maintain the current split rate and reduce the risk of intermittent shortages by increasing donor retention. Studies

have shown that double and triple platelet collections proportionately extend the time that donors are on the apheresis machine and increase the proportion of donors reporting adverse events, such as headaches, cramps, paresthesias, phlebotomy site hematomas, dizziness, faints, and so on.<sup>20,21</sup> Donors who suffer adverse events are more likely to discontinue a collection procedure and are less likely to return to donate again.<sup>20</sup> Concerns about donor safety have led the FDA to restrict the frequency of double and triple platelet collections in the United States to once every 7 days, and to a restriction by the German authorities to a maximum yield per apheresis donation of  $8 \times 10^{11}$  platelets.<sup>22-24</sup> It is notable that the German restriction would prevent the collection of triple apheresis PCs if implemented in the United States but are compatible with triple collections under the German minimum standard of  $2.0 \times 10^{11}$  platelets/unit (Table 2).

### Impact on patients

Lowering the standard minimum content of platelets may directly benefit patients by increasing overall platelet availability, reducing intermittent shortages and balancing the platelet supply over time. Potential downsides are that lower doses may be associated with an increased risk of hemorrhage for some indications, shorter intertransfusion intervals, and a need for an increased number of transfusions and donor exposures, each with a risk of relevant transfusion-transmitted infection and transfusion reactions.

With respect to bleeding, the PLADO study<sup>1</sup> found no effect of platelet dose on the primary endpoint, the proportion of patients experiencing World Health Organization Grade 2 or higher bleeding (where Grade 2 represents clinically significant bleeding not requiring immediate RBC transfusion; e.g., oropharyngeal bleeding or epistaxis [ $>30$  min within 24 h], purpura [ $>1$  in], deep hematoma, etc.). Grade 2 bleeding was observed in 71%, 69%, and 70% of the patients in the low-, medium-, and high-dose groups, respectively. The incidence of higher (i.e., more clinically significant) grades of bleeding that required immediate transfusion (Grade 3) or were life threatening (Grade 4) and other adverse events were similar among the three groups.

Low-, medium-, or higher-dose therapy was defined as  $1.1 \times 10^{11}$ ,  $2.2 \times 10^{11}$ , or  $4.4 \times 10^{11}$  platelets/m<sup>2</sup> BSA, respectively. This translates into median doses for a 70-kg man with a 1.9 m<sup>2</sup> BSA of  $2.1 \times 10^{11}$ ,  $4.2 \times 10^{11}$ , and  $8.4 \times 10^{11}$  platelets, a range that is much broader than the proposed reduction in minimal PC content of  $3.0 \times 10^{11}$  or more to  $2.5 \times 10^{11}$  or more platelets (Fig. 2). The figure shows graphically the change in overall total platelet dose, intertransfusion interval, and number of platelet transfusions in the PLADO study,<sup>1</sup> suggesting that the impact of a reduction to a minimal content of  $2.5 \times 10^{11}$  or more platelets would only modestly decrease the intertransfusion interval and increase the number of transfusions required. The total number of platelets used would also be modestly reduced. The median number of platelets

transfused was significantly lower in the low-dose group ( $9.25 \times 10^{11}$ ) than in the medium-dose group ( $11.25 \times 10^{11}$ ) or the high-dose group ( $19.63 \times 10^{11}$ ) ( $p = 0.002$  for low vs. medium,  $p < 0.001$  for high vs. low and high vs. medium), and the median number of platelet transfusions given was significantly higher in the low-dose group (five vs. three in the medium-dose and three in the high-dose group;  $p < 0.001$  for low vs. medium and low vs. high).<sup>1</sup> Simply put, the PLADO study needed to use two- and fourfold increases to have sufficient power to demonstrate dose effects, a differential far in excess of the approximately 17% decrease in PC content that we propose. From this we conclude that a requirement for an increase in the number of doses or reduced transfusion interval may be acceptable, if it is indeed measurable at all, especially as the average dose transfused will by necessity remain higher than the minimally required PC content.

The PLADO study has been criticized as not generalizable to other indications, given that it was limited to hospitalized hematology/oncology patients who mostly require platelet transfusion for prophylaxis. It is notable therefore that approximately 70% of PLADO patients experienced Grade 2 or higher bleeding on an average of approximately 17% of study days.<sup>1</sup> Platelets were transfused for therapeutic (as opposed to prophylactic) benefit in this setting and, no excess in mortality, Grade 3 or 4 bleeding, or RBC transfusions were noted between the groups. There are no randomized controlled trials evaluating the safety of lower-content PCs in the surgical or acute trauma setting; nevertheless, extensive experience in countries that routinely use lower PC content does not suggest a detrimental effect. Likewise, there are no randomized controlled studies evaluating lower-content platelets in platelet additive solution (PAS) or pathogen-reduced platelets; however, routine experience in countries that allow lower content than the United States, such as France ( $2.0 \times 10^{11}$  minimum content) and Switzerland ( $2.4 \times 10^{11}$  minimum content) has not indicated an increase in excessive bleeding with the use of pathogen-reduced platelets in PAS.<sup>25-28</sup> Regardless, hospital physicians will need to be educated as to the decreased average content of PCs and to pay attention to the actual dose of platelets given in each transfusion.

With respect to pathogen-reduced platelets, 12 completed studies summarized in a meta-analysis of two technologies (including 3 randomized controlled trials) confirmed no increased risk of clinically significant or severe bleeding.<sup>26,29-31</sup> A recent large randomized controlled trial by Garban et al.<sup>32</sup> comparing the use of untreated platelets suspended in plasma or PAS and pathogen-reduced platelets suspended in PAS reported more frequent transfusions of lower-dose pathogen-reduced platelets, but found no significant difference in the total number of platelets transfused per patient. This study did not report any statistically significant difference in the incidence of grade 2 or higher (43.5%, 45.3%, and 47.9%, respectively;  $p$  value not reported) or severe grade 3 or higher (9.5%, 11.7%, and

**TABLE 3. Rates per million of septic transfusion reactions and confirmed positive bacterial culture screens with >2.1 million platelet collections and ~4 million PC at the American Red Cross Blood Services.<sup>35</sup>**

	Collections (2007-2011)			Odds Ratio (95% C.I.)*
	Single	Double	Triple	
Septic transfusion reactions per million	8.9	15.5	27.1	3.05 (1.06-9.90)
Confirmed positive bacterial cultures per million	163	179	268	1.65 (1.27-2.10)

\* Confidence Interval. The odds ratios depict the comparison of triple and single collections, and are statistically significant ( $p < 0.05$ ) for both sepsis and confirmed positive bacterial cultures.

9.9%, respectively;  $p = 0.68$ ) bleeding among the three study arms. With a prespecified margin of 12.5%, noninferiority for Grade 2 or higher bleeding was not achieved when pathogen-reduced platelets suspended in PAS were compared with untreated platelets suspended in plasma (4.4%; 95% confidence interval; -4.1% to 12.9%) but was achieved when the pathogen-reduced platelets suspended in PAS were compared with untreated platelets suspended in PAS (2.6%; 95% confidence interval; -5.9% to 11.1%). This non-inferiority study was designed with a relatively low statistical power of 80% for demonstrating noninferiority for the primary outcome between the pathogen-reduced platelets suspended in PAS arm and each of the 2 control arms, assuming a 60% incidence rate of grade 2 or higher bleeding and 810 enrolled patients. Power was further impacted by the enrollment of only 790 patients and the lower actual incidence of bleeding (43%-48%) in the study.

### Impact on platelet safety

Over the past decade, blood centers have increased the proportion of multiple-unit apheresis PC collections to increase operational efficiency, minimize donor exposures, and meet hospital demand. All plateletpheresis collections are screened by culture for bacteria before release to hospitals (or an increasing number are pathogen reduced). In 2008, the American Red Cross began systematically collecting triple apheresis collections from an increasing proportion of donations, such that by 2010, more than 25% of their donors gave three units at each collection (R. Benjamin, unpublished data). This coincided with an approximately 20%

overall increase in the confirmed positive bacterial culture rate per collection (166 per  $10^6$  collections in 2006-2008; 208 per  $10^6$  collections in 2010-2014).<sup>33,34</sup> The American Red Cross reports that triple platelet collections are more likely to be contaminated with bacteria on routine postcollection bacterial culture screening and are more likely to be associated with patient septic transfusion reactions (Table 3).<sup>35</sup> As published first by others and confirmed by the American Red Cross based on their data set, one apheresis technology was more often associated with bacterial contamination, raising the possibility that the effect of multiple collections may apply differentially based on that apheresis technology.<sup>34,36</sup> The difference between apheresis technologies was reversed before the implementation of triple platelet collections (Table 4),<sup>33</sup> further supporting the concept that the increase was related to the proportion of triple platelet collections. While the cause of this association is not known, it is possibly related to the increased duration of the collection procedure and the need to process increased donor blood volumes to harvest more platelets. It is possible, therefore, that a reduced duration of platelet collections with reduced processed blood volume may be associated with less bacterial contamination of platelet components.

Bacterial contamination of platelets is recognized as a serious risk of transfusion and the FDA Blood Products Advisory Committee has endorsed interventions that may further strain the platelet supply.<sup>37</sup> Delayed, large-volume bacterial cultures consume 3.8% to 10% of each PC (e.g., up to 16-20 mL from each approx. 200-mL split PC),<sup>38,39</sup> while pathogen reduction treatment incorporates similar processing losses that complicate the ability to treat sufficient

**TABLE 4. Rates per million of positive bacterial culture screens by apheresis technology, as published by Eder et al.<sup>33,34</sup>**

	Time period	Apheresis Technology		Overall % Triple Collections
		Trima	Amicus	
(Number of collections) Confirmed positive bacterial cultures per million	2006-2008*	(118,014) 229	(647,900) 159	0%
	2010-2014†	(671,955) 112	(1,486,888) 252	~25 - 30%

\* Calculated from data from Table 3 in Eder et al. 2009 after the introduction of universal inlet line sample diversion and 8 ml aerobic bacterial culture screening<sup>33</sup>

† Eder et al. 2017<sup>34</sup>

platelets within the configuration of the current processing sets. A lower minimum platelet content will facilitate the introduction of both large-volume culture or pathogen reduction, as implemented in the United Kingdom, France, and Switzerland, respectively. These countries require PCs to contain  $2.0\text{--}2.5 \times 10^{11}$  or more platelets today (Table 1). Any change in the standard requirement for conventional PCs would only apply to pathogen-reduced PCs in the United States if additional specific changes in the instructions for use were approved by the FDA.

### Impact on hospitals

As outlined above, hospitals could benefit from reduced apheresis platelet content through the increased availability of platelets and in the outpatient setting if the selective use of multiple PC transfusions proves to be cost beneficial. On the inpatient side, reduced platelet content could decrease the intertransfusion intervals and increase the number of transfusions, increasing the corresponding workload for laboratory and nursing staff. Our analysis of the PLADO data (Fig. 2) suggests that this would be a small effect, if it is measurable at all. Nevertheless, if the platelet content of each PC is required to be on the label, there is an opportunity to mitigate the increased hospital burden: Over the prior decade, hospitals reduced their usage of RBC concentrates by approximately 30% by developing evidence-based, generally lower, transfusion triggers for a spectrum of patient populations. Similar to RBC consumption 10 years ago, the United States currently has one of the highest per capita usage rates of PCs (Fig. 1). There is an opportunity to develop evidence-based guidelines for platelets with appropriate dosing based on clinical and patient factors, to improve patient care and reduce hospital costs. PCs contain a range of platelet contents, with only the minimum platelet content as a quality control requirement. Research is needed to tailor specific platelet content to the clinical situation, in so doing possibly reducing overall PC usage. Labeling each PC with the actual platelet content would facilitate such studies.

## CONCLUSIONS

There is a strong rationale for reducing the US minimum apheresis PC content requirement to align with international practice. The US has among the highest per capita use and highest minimum PC content in the world. Recurrent local and regional shortages are frequent, and this may be due in part to the pressure put on donors needed to fulfill the ongoing demand. The PLADO study demonstrated the comparable efficacy of low-, medium-, and high-dose platelet doses in terms of both the treatment and prevention of bleeding, albeit only in the setting of hospitalized patients who are thrombocytopenic from marrow hypoplasia. Outside of this setting there are few definitive studies to suggest

the optimal platelet transfusion trigger, PC dose, or treatment regime. An immediate requirement for the PC content to be stated on the container would allow physicians to begin considering dose in the patients' management. With a lower minimum content requirement, immediate benefits would be an increase in PC availability, reduced pressure on donors to contribute large apheresis donations, and/or perhaps improved safety. While there has been much emphasis on single-unit administration for RBCs and platelets in recent years, in certain clinical situations (e.g., transfusion-dependent outpatients) multiple doses of platelets may be beneficial. Research should be sponsored to identify optimal platelet transfusion thresholds and dosing strategies for nonhospitalized patients for prophylactic use, in the presence of congenital or acquired platelet dysfunction and for bleeding patients in surgical and trauma settings.

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## CONFLICTS OF INTEREST

R.J.B. is an employee of Cerus Corporation, a manufacturer of pathogen inactivation technologies. E.K.W. owns stock in Cerus. The other authors have disclosed no conflicts of interest.

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