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Blood Still Kills: Six Strategies to Further Reduce Allogeneic Blood Transfusion-Related Mortality

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After reviewing the relative frequency of the causes of allogeneic blood transfusion-related mortality in the United States today, we present 6 possible strategies for further reducing such transfusion-related mortality. These are (1) avoidance of unnecessary transfusions through the use of evidence-based transfusion guidelines, to reduce potentially fatal (infectious as well as noninfectious) transfusion complications; (2) reduction in the risk of transfusion-related acute lung injury in recipients of platelet transfusions through the use of single-donor platelets collected from male donors, or female donors without a history of pregnancy or who have been shown not to have white blood cell (WBC) antibodies; (3) prevention of hemolytic transfusion reactions through the augmentation of patient identification procedures by the addition of information technologies, as well as through the prevention of additional red blood cell alloantibody formation in patients who are likely to need multiple transfusions in the future; (4) avoidance of pooled blood products (such as pooled whole blood–derived platelets) to reduce the risk of transmission of emerging transfusion-transmitted infections (TTIs) and the residual risk from known TTIs (especially transfusion-associated sepsis [TAS]); (5) WBC reduction of cellular blood components administered in cardiac surgery to prevent the poorly understood increased mortality seen in cardiac surgery patients in association with the receipt of non–WBC-reduced (compared with WBC-reduced) transfusion; and (6) pathogen reduction of platelet and plasma components to prevent the transfusion transmission of most emerging, potentially fatal TTIs and the residual risk of known TTIs (especially TAS).

ONLY OVER THE last 5 years have measures been implemented to reduce the risks of 2 of the 3 leading causes of transfusion-related deaths; these are the risks of transfusion-related acute lung injury (TRALI) and transfusion-associated sepsis (TAS). Together with ABO and non-ABO hemolytic transfusion reactions (HTRs), these 3 appear to be the most common causes of allogeneic blood transfusion (ABT)-related mortality seen in the United States today.[1] Although the etiology of these risks had been known for years[2-4] and measures for their prevention had been advocated previously,[5,6] it was only in March 2004 and November 2006, respectively, that the AABB (formerly the American Association of Blood Banks) recommended that blood establishments limit and detect bacterial contamination in all platelet components,[7] as well as collect fresh frozen plasma (FFP) and single-donor platelets solely from male donors (or female donors without a history of pregnancy or shown not to have white blood cell [WBC] antibodies).[8]

Bacterial contamination of blood components results from the introduction of low concentrations of skin bacteria at the time of phlebotomy, less commonly from asymptomatic donor bacteremia, or rarely during blood processing.[9] Before various process improvements started to be introduced around 2004, platelets and red blood cells (RBCs)

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were, respectively, responsible for 70% and 30% of fatalities from TAS.[9] This is because platelets are stored at room temperature—allowing for bacterial proliferation—and also because platelets are more often given to patients susceptible to bacterial infection, that is, to neutropenic subjects who also often have an impaired immune system. Accordingly, most efforts to reduce the risk of TAS have hitherto specifically targeted platelet components.[7]

The efforts to reduce the risk of TRALI have targeted specifically FFP and single-donor platelets.[8] This is because, depending on how TRALI is defined,[10,11] WBC alloantibodies are identified in 25% to 90% of the donors implicated in TRALI cases.[12] Such donor antibodies are believed to attack the recipient's WBCs in the microcirculation of the lungs, causing noncardiogenic pulmonary edema.[2,5] Most donors implicated in TRALI have been multiparous women alloimmunized to paternal WBC alloantigens during pregnancy.[13] Blood products containing a large volume of plasma from an individual donor, thus, could contain a large amount of a WBC antibody directed against a cognate WBC antigen of a particular transfusion recipient. As a result, such products could be more likely to cause TRALI than products containing a small volume of plasma if transfused into a recipient carrying the corresponding WBC alloantigen.[5] This possibility led to the recommendation that FFP and single-donor platelets be collected solely from male donors (or female donors without a history of pregnancy or shown not to have WBC antibodies).[8]

It was the hemovigilance reports from France,[14] the United Kingdom,[15,16] and the province of Quebec in Canada,[17] along with the reports on transfusion-related deaths from the US Food and Drug Administration (FDA),[1,4,18-21] that focused our attention on TAS and TRALI, along with HTRs, as the major contemporary causes of ABT-related mortality and major morbidity. These reports[1,4,14-21] and the ensuing mandates[7,8] resulted in the risks of TAS and TRALI being at least partly addressed over the last 5 years, although the risk of HTRs still remains to be directly confronted.

Well into the 1990s, the attention of transfusion medicine professionals remained concentrated on the morbidity and mortality associated with transfusion-transmitted infections (TTIs). Although only 3 years had elapsed between the recognition of the threat that the human immunodeficiency virus (HIV) posed to blood safety (1982) and the implementation of donor testing (1985), approximately 12 000 cases of transfusion-acquired HIV infection were estimated to have occurred in the United States.[22] When the interval between recognition and introduction of testing was longer, the number of transfusion-acquired infections was correspondingly higher. Thus, in 1970 to 1990, there were 4.8 million cases of hepatitis C virus (HCV) transmitted through ABT.[23] Even if only 3% of these resulted in fatal cirrhosis or hepatocellular carcinoma in long-term survivors,[24] and if only 30% of transfusion recipients survived long enough to develop such complications,[25] 43 200 ABT-related deaths could still have ensued.[26]

This mortality from TTIs before the 1990s dwarfed the concomitant mortality from TRALI, TAS, and HTRs, focusing blood safety efforts toward the prevention of TTIs. As a result, the past 2 decades have witnessed an impressive reduction in the probability of transmission of HIV and HCV through ABT by up to 4 log.[27] Although the risks of TTIs have been greatly reduced, the risk of a new, or poorly understood, infectious disease with a long incubation period that can be transmitted by ABT, while it is accumulating in the blood donor base before its clinical consequences become apparent, remains a "fixed and inevitable property of transfusion medicine."[28] Thus, ABT can still transmit lethal infections due to known pathogens, especially bacteria,[1,14,16,21] even while novel transfusion-transmitted, or potentially transfusion-transmitted, pathogens continue to emerge.[29]

In addition to the deaths caused by the noninfectious and infectious complications of ABT, there are also deaths attributed to ABT by observational studies and randomized controlled trials (RCTs) through pathophysiologic mechanisms that we do not yet understand. In particular, RCTs comparing cardiac surgery patients randomized to receive non–WBC-reduced RBCs vs RBCs from which the WBCs had been removed by WBC reduction filters have attributed increased mortality to the receipt of non–WBC-reduced (compared with WBC-reduced) ABT.[30-32] Non–WBC-reduced (compared with WBC-reduced) ABT has not been associated with a defined cause(s) of death in these RCTs.[33] Nevertheless, the magnitude of the absolute risk reduction attributed to WBC reduction in the RCT of van de Watering et al[30] was impressive, a statistically significant greater mortality of 7.8% vs 3.5%, in subjects receiving non–WBC-reduced vs WBC-

reduced RBCs, respectively. Although overall mortality has been lower in the United States[32] than reported in the Dutch[30,31] RCTs, such potentially WBC-mediated adverse ABT effects[30-32] could account for a larger number of ABT-related deaths than all the currently established complications of ABT combined!

Observational studies comparing transfused and untransfused patients[34-38] have also reported increased mortality in association with ABT per se, independently of the receipt of non–WBC-reduced vs WBC-reduced RBCs. In the Transfusion Requirements in Critical Care (TRICC) RCT patients allocated to receive RBC transfusion based on restrictive vs liberal transfusion criteria demonstrated a trend ($P = .11$) toward increased 30-day mortality, as well as increased in-hospital mortality ($P = .05$), in association with greater exposure to ABT in the liberal transfusion arm.[39]

This review will thus present estimates of the mortality from infectious and noninfectious ABT complications in the United States today and will advocate for the adoption of 6 specific interventions to prevent transfusion-related deaths. In particular, these 6 strategies to further reduce ABT-related mortality will be assessed for their impact upon reducing deaths from ABT.

SOURCES OF DATA AND THEIR INTERPRETATION

Data on transfusion complications, including deaths from transfusion complications, come from passive surveillance ("hemovigilance") studies, active surveillance studies, as well as both RCTs and observational studies. Both the observational studies and the RCTs evaluate consecutive transfused patients at a particular setting(s) as part of a research protocol and—in theory—would be expected to produce the most reliable data. Their downside, however, is that they usually enroll a number of transfused patients that is much too small to document the incidence of rare transfusion complications (or the risk of death from ABT). Active surveillance studies are conducted at a particular hospital or at "sentinel" sites in which there is heightened awareness of, and special arrangements have been made for detecting, usually a specific transfusion complication. Passive surveillance systems rely on passive (and often voluntary) reporting of adverse events associated with ABT, including ABT-related deaths. Such hemovigilance systems have been in place in various countries—including France,[14] the United Kingdom,[15,16] other European countries, and the province of Quebec[17] in Canada. No coordinated hemovigilance system exists yet in the United States, although a pilot program was recently introduced.[40] Moreover, the reporting of all identified transfusion-related deaths to the FDA has been required since 1976.[1,4,18]

Reporting to hemovigilance systems can be mandatory (as it is in France[14]) or voluntary (as it used to be in the United Kingdom until recently[16]). Adverse events, including deaths, captured by these systems depend on whether a particular adverse event caused by a transfusion was suspected of being, investigated as possibly being, and/or deemed to be transfusion related based on the criteria used locally for the diagnosis of each specific transfusion complication. Whether ABT is considered as the possible cause of an adverse event or death varies with the medical and nursing staff awareness of transfusion complications at each particular clinical setting, as well as with local culture, resources, and logistics vis-à-vis the extent of the investigation and the reporting of such adverse events along the designated channels of the hemovigilance system.

Thus, hemovigilance systems tend to greatly underestimate the incidence of ABT-related adverse

Table 1. Effect of the Source of the Data on the Reported Incidence of TRALI

Source of data (diagnostic criteria for TRALI)	Reported incidence of TRALI
Passive surveillance system[41] (using the Canadian consensus criteria[11])*	1 per 15 924 for FFP 1 per 40 452 for pools of 5 whole-blood-derived platelets 1 per 44 092 for RBCs 1 per 46 996 for single-donor platelets
Active surveillance system[42] (study conducted before the Canadian consensus criteria were promulgated)	1 per 432 for pools of whole blood–derived platelets 1 per 1224 for single-donor platelet concentrates 1 per 4410 for RBCs 1 per 19 411 for FFP
Observational study[43] (using the Canadian consensus criteria in an ICU setting)	TRALI diagnosed in 74/901 (8.2%) sequentially admitted patients who received transfusions of multiple blood components (ie, RBCs, FFP, single-donor platelets, and platelet pools)

* The figures in this article[41] are reported separately for 2004 and 2005; the 2005 figures are given here.

events. Table 1 contrasts the incidence of TRALI reported by a passive surveillance sytem,[41] an active surveillance system initiated at a particular hosptial,[42] and an observational study of critically ill patients admitted to an intensive care unit (ICU).[43] The hemovigilance[41] and observational[43] studies based their diagnoses of TRALI on the Canadian consensus criteria[11] promulgated by the Canadian Consensus Conference in 2004, whereas the study using an active surveillance system[42] had been conducted earlier—at a time when there was no standard definition of what constellation of findings qualified as definite or possible TRALI. The 2 surveillance studies[41,42] encompassed all transfused patients, whereas the observational study of ICU patients[43] included only critically ill patients.

This is especially important because TRALI is believed to result from an interplay of both patient- and transfusion-related factors and may thus be much more common in critically ill (than other transfused) patients. Critically ill patients may also have a lower threshold for TRALI than the average transfusion recipient[44] because of sepsis, trauma, and other factors that may represent the "first hit" in the "2-hit" hypothesis of TRALI pathogenesis.[45,46] In such critically ill patients, too, many cases of acute lung injury (ALI)—occurring in the presence of one or several alternate causes of ALI—can be misdiagnosed as TRALI because of a merely temporal association with ABT.

Thus, the more than 1000-fold difference in the reported incidence of TRALI between the hemovigilance[41] and observational[43] studies shown in Table 1 is due partly to the design used (passive surveillance vs observational) and partly to patient factors and/or cases of ALI being misdiagnosed as TRALI in multiply-transfused patients (in whom respiratory distress happens to manifest itself within 6 hours of a transfusion). The relevance of the patient factors notwithstanding, however, because both studies[41,43] used the same criteria[11] for diagnosing TRALI, Table 1 underscores the extent to which passive surveillance data may underestimate the incidence of serious ABT complications.

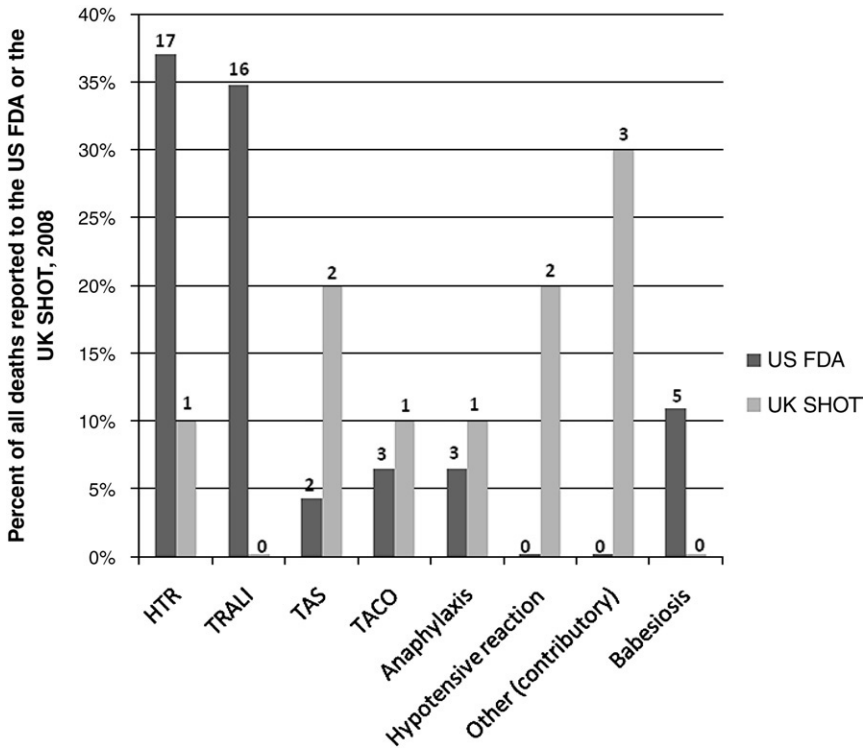

Fig 1. Causes of ABT-related deaths as a proportion of all deaths reported to the US FDA or the United Kingdom SHOT in 2008. The number of deaths related to transfusion (US FDA), or in which transfusion was deemed to have a causal or contributory role (United Kingdom SHOT), is shown above each column. Only 1 death (secondary to a septic reaction to platelets) was deemed to have been caused by an ABT in the United Kingdom. In all other cases (including 2 cases of inappropriate transfusion and 1 febrile, nonhemolytic transfusion reaction), the transfusion was deemed only to have contributed to a patient's death.

When awareness of transfusion complications increases, or when resources are expended to detect transfusion complications, reporting of transfusion complications to hemovigilance systems increases. Both of these conditions were satisfied, before the implementation of bacterial detection in platelets, at the Johns Hopkins Hospital (Baltimore, MD).[47,48] Over 12 years, Ness et al[47] had implemented a system of prospective monitoring, whereby all febrile transfusion reactions to platelets were assessed by culture. Starting from a baseline of 51.7% of the therapeutic platelet doses at their hospital provided as single-donor platelets, they observed that—as the proportion of therapeutic platelet doses provided as single-donor platelets (as opposed to platelet pools) increased from 51.7% to 99.4%—the risk of TAS declined from 1 in 4818 to 1 in 15 098 platelet transfusions.[47] This 3-fold decrease in risk could be extrapolated to a 5-fold reduction (with an expected risk of TAS of 1 per 3000 platelet pools) had the authors started from no therapeutic platelet doses provided as single-donor platelets.[47,48] A virtually identical risk (1 per 2282 platelet pools in 2000 and 1 per 4149 platelet pools in 2001) was observed during the first 2 years of the Quebec hemovigilance program, which relied on hospitals that cultured 40.4% to 51.6% of platelet pools implicated in transfusion reactions and that were staffed with transfusion officers.[17] In contrast, in 1994 to 1998, the French hemovigilance system—probably the most comprehensive passive surveillance system that entailed mandatory reporting—observed a risk of sepsis secondary to platelet transfusion—if pools of 6 platelet concentrates are assumed—of only 1 per 13 000 platelet pools.[14] The reported risk was far lower in the United Kingdom hemovigilance program.[15,16]

Data from hemovigilance systems must therefore be interpreted in the light of this "passive surveillance artifact" that results in the underreporting of the overall adverse transfusion events, along with the relative overreporting of specific transfusion complications (of which the medical and nursing staff become more aware at one time or another) compared with all other transfusion complications. Influential publications in the literature and high-profile preventive efforts initiated by national blood safety agencies or professional societies, heighten clinicians' awareness of specific ABT complications, generating more diagnoses of those particular ABT-related adverse events and more reporting of such events to the hemovigilance systems.

OVERVIEW OF THE FINDINGS OF TWO MAJOR PASSIVE SURVEILLANCE SYSTEMS

In 2008, 46 fatalities reported to the US FDA[1] were deemed to be transfusion related, and ABT was deemed to have a causal or contributory role in 10 deaths reported to the United Kingdom Serious Hazards of Transfusion (SHOT) System.[16] Given that the population of the United States is 5 times larger than the population of the United Kingdom, the 2 passive surveillance systems seem to have recorded a similar number of transfusion-related deaths per million population. Also, most of the differences in the frequency of the specific causes of transfusion-related deaths (Fig 1) could be due to chance because transfusion-related deaths captured by passive surveillance systems are exceedingly rare events. Nonetheless, transfusion-transmitted babesiosis occurs only in the United States (where *Babesia* species are endemic), and—depending on what assumptions about appropriate probability distributions are made—the differences in mortality from TRALI and HTRs probably exceed the figures that could be expected solely from the play of chance.

In 2005 to 2008, TRALI, HTRs, and TAS ranked, respectively, as the first, second, and third most

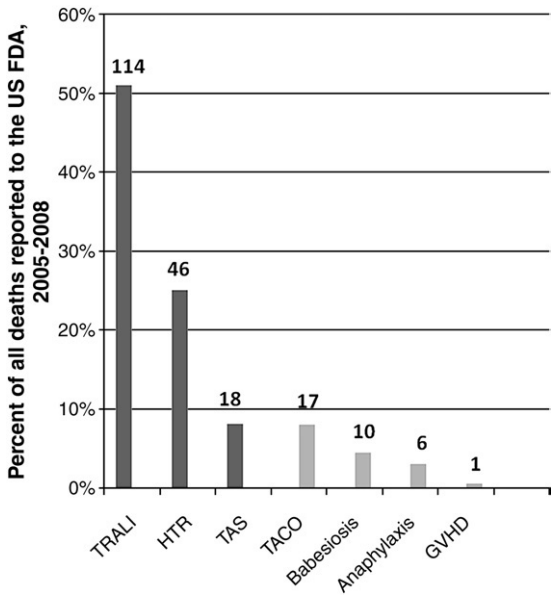

Fig 2. The 3 leading causes of ABT-related deaths, along with all other causes of ABT-related deaths reported to the US FDA for the last 4 years (2005-2008). The figure shows the proportion of all deaths reported to the US FDA in 2005 to 2008 that was attributed to each cause of transfusion-related mortality. The actual number of deaths from each cause is shown above the corresponding column.

frequent cause of transfusion-related mortality in the United States (Fig 2). Together, these 3 causes of death accounted for 84% (178/212) of all fatalities reported to the US FDA. The remaining deaths were due to transfusion-associated circulatory overload (TACO), transfusion-transmitted babesiosis, anaphylaxis, or graft-vs-host disease (GVHD).[1]

When the number of deaths from the 3 leading causes of transfusion-related mortality in the United States was compared between 2004 to 2008 and 2001 to 2003, TRALI appeared to have displaced HTRs as the leading cause of transfusion-related mortality (Fig 3). The FDA alerted transfusion medicine professionals in the United States to the possibility that transfused patients may be at increased risk of TRALI on October 19, 2001.[49] Between 1992 and 2001, the FDA had received 45 reports of transfusion-related fatalities secondary to TRALI, and—at that time—TRALI was thought to be the third leading cause of transfusion-related mortality in the United States. As the FDA had not received any reports of TRALI fatalities before 1992, they ascribed the increase in the number of received reports of deaths due to TRALI to better recognition and reporting of TRALI.[49] The overall limited awareness of TRALI as a transfusion complication and as a clinical entity separate from the acute respiratory distress syndrome[50-52] (ARDS—from which TRALI is often clinically indistinguishable) is underscored by the fact that TRALI was not identified as a specific transfusion complication by the French hemovigilance system in 1994 to 1999.[14]

Around 2004, TRALI awareness increased by the publicity associated with the United Kingdom decision to convert to "male-only" FFP to mitigate the risk of TRALI (October 2003)[16] and by the publicity associated with the Canadian Consensus Conference on TRALI convened to generate a standardized definition of TRALI (April 2004), followed by the promulgation of the consensus criteria for the diagnosis of TRALI (December 2004).[11] At approximately the same time, the AABB standard that blood establishments limit and detect bacterial contamination in all platelet components became effective (March 2004).[7] Various other process improvements were also implemented to reduce the risk of TAS secondary to platelet transfusion.[9] The presumed increase in TRALI awareness and the measures to reduce TAS were temporally associated with an increase in the

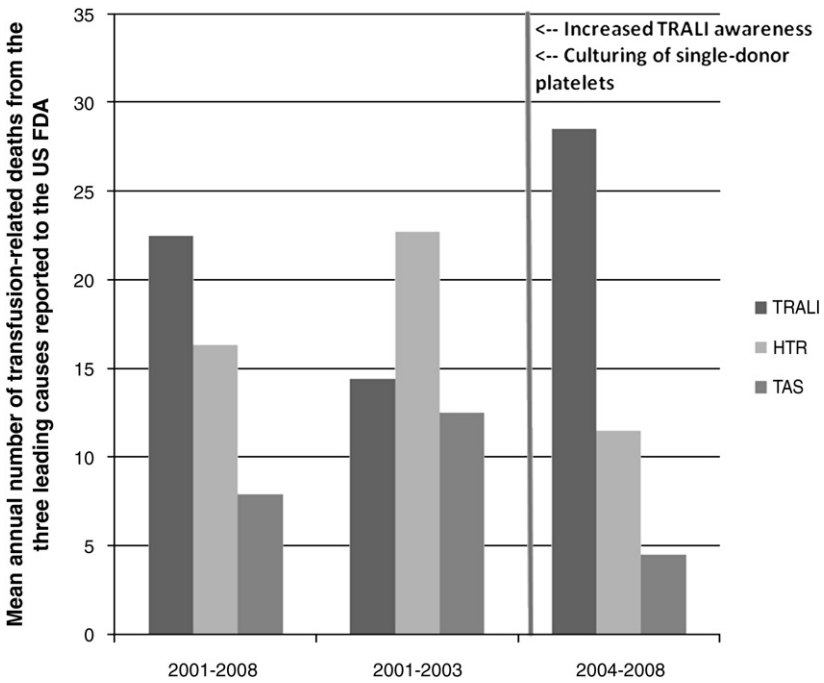

Fig 3. The leading causes of ABT-related deaths reported to the US FDA in 2001 to 2008 showing a comparison of the number of deaths attributed to these causes in 2001 to 2003 vs 2004 to 2008. For each time period, the figure shows the mean annual number of deaths deemed to be due to TRALI, TAS, or HTR.

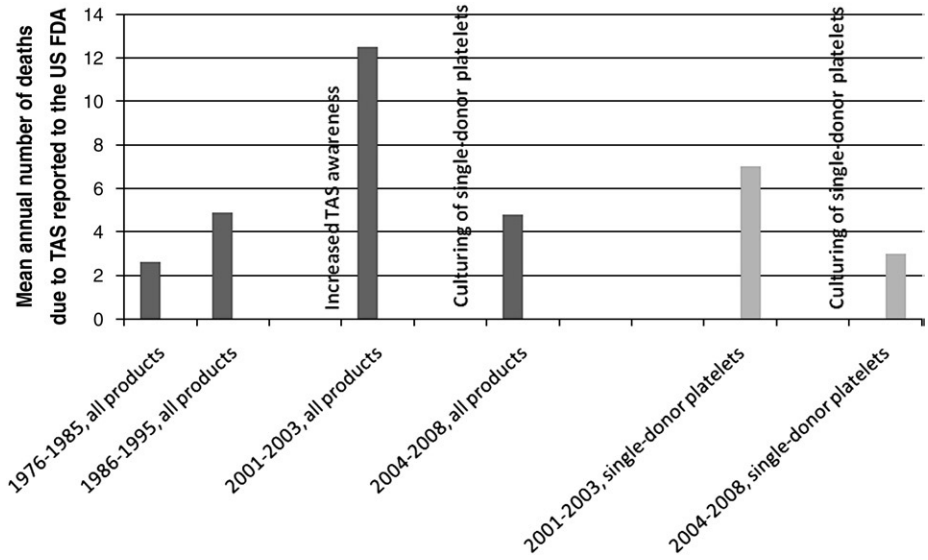

Fig 4. A comparison of the number of deaths from TAS between 2001 to 2003 and 2004 to 2008 shown separately for all transfused products and for single-donor apheresis platelets. For each period, the figure shows the mean number of deaths deemed to be due to TAS each year based on the reports of transfusion-related fatalities made to the US FDA. Data are also shown for the earlier periods of 1976 to 1985 and 1986 to 1995, but the data for 1996 to 2000 have not been made available.

reporting of deaths from TRALI, as well as a reduction in the reporting of deaths from TAS (Fig 3).

Awareness of the risk of TAS had been increasing before 2001, culminating in an FDA/Center of Biologics Evaluation and Research Workshop where the data on 26 fatalities from transfusion of contaminated RBCs and 51 fatalities from transfusion of contaminated platelets in 1976 to 1998 were presented (September 1999).[53] Already in 1996, as the risks of transfusion-transmitted HIV and HCV infection had declined, the AABB had alerted transfusion medicine professionals that the risk of receiving bacterially contaminated platelets might be 50- to 250-fold higher than the combined risk of HIV, hepatitis B virus (HBV), HCV, and human T-lymphotropic virus (HTLV) transmission through transfusion.[54]

The reduction in the reporting of deaths from TAS to the US FDA starting in 2004 is evident both for all transfused products and specifically for single-donor platelets (Fig 4). In March 2004, automated bacterial culture systems were available only for single-donor platelets collected by apheresis. Hospitals releasing pooled whole blood–

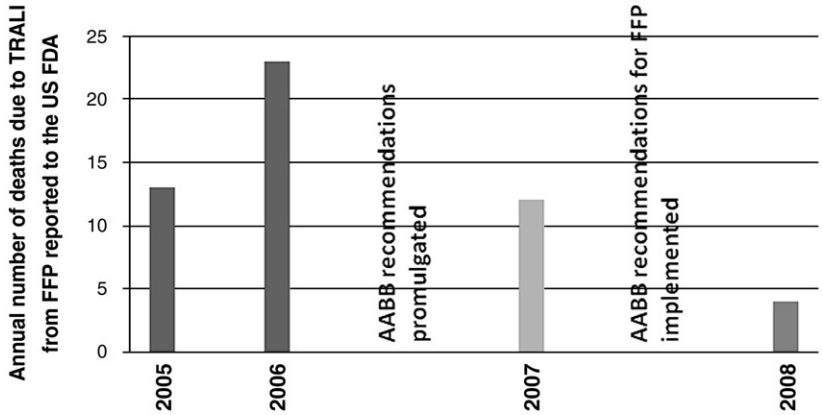

Fig 5. Comparison of the number of deaths from TRALI associated with the transfusion of FFP between 2005 to 2007 and 2008. For each year, the number of deaths reported to be due to TRALI is based on reports of transfusion-related fatalities made to the US FDA.

derived platelets for transfusion had to use surrogate methods for bacterial detection,[9] the sensitivity of which was 4.6 times less than that of bacterial culture.[55] Accordingly, to comply with the "spirit" rather than the "letter" of the March 2004 AABB standard, US blood establishments moved voluntarily toward the provision of single-donor (rather than pooled whole blood–derived) platelets for transfusion. Thus, in 2006, 87.5% of all therapeutic platelet doses transfused in the United States were provided as single-donor platelets.[56]

By November 2007, virtually all FFP transfused in the United States was collected from male donors,[8] although the AABB recommendation that single-donor platelets be collected from male donors or female donors without a history of pregnancy or shown not to have WBC antibodies had not been implemented by November 2008 (as it was originally intended),[8] neither has it been implemented consistently across the United States as of this writing (October 2009). Accordingly, any impact of the November 2006 AABB recommendations for TRALI prevention[8] should be reflected solely on the TRALI cases recorded in 2008 in association with transfusion of FFP.

Figure 5 shows that the conversion to male-only FFP in the United States was temporally related to a reduction in the number of TRALI deaths associated with FFP transfusion reported to the FDA. The variation in the number of TRALI deaths attributed to FFP reported between 2005 and 2008 could be due to chance or, alternatively, to increasing awareness in 2005 to 2006 of the risk of TRALI specifically associated with FFP transfusion, followed by a reduction in the number of TRALI deaths in 2007 to 2008 when female FFP was gradually replaced by male FFP. Increasing awareness in 2005 to 2006 of the risk of TRALI specifically related to transfusion of FFP is possible—associated with the publicity generated by the conversion to male-only FFP in the United Kingdom in 2003 to 2004, as well as United Kingdom studies of TRALI that had considered as the "at-risk" patient population the recipients of solely FFP.[57]

A reduction in the number of deaths from TRALI had already been observed in the United Kingdom that had gradually moved to male-only FFP in 2003 to 2004, without replacing existing FFP inventories (or mandating 100% compliance with the policy that plasma for transfusion be collected solely from male donors). Awareness of the risk of TRALI in the United Kingdom may have thus preceded that in the United States by approximately 3 years, as did the policy to convert to male-only FFP. After the conversion, the annual number of deaths from TRALI reported to the United Kingdom SHOT system declined (Fig 6) until in 2008, for the first time since reporting to the SHOT system started in 1996, no death from TRALI was recorded in the United Kingdom. There were 3 nonfatal cases of TRALI reported in 2008, and all 3 were due to transfusion of FFP from female donors in England (where the use of male donors for FFP is not yet

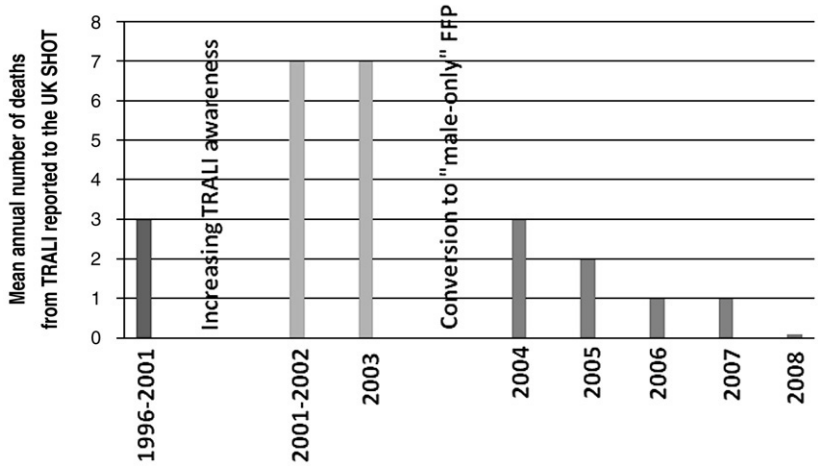

Fig 6. The number of deaths from TRALI for 12 years (1996-2008) of reporting to the United Kingdom SHOT system. For each period, the figure shows the mean annual number of deaths deemed to be due to TRALI based on the reports of transfusion-related fatalities made to the United Kingdom SHOT program. There were zero (0) fatalities from TRALI in 2008.

universal).[16] By comparison, 7 of the 12 transfusion-related deaths reported to the United Kingdom SHOT system in 2003 had been due to TRALI.[16]

Comparisons of the figures obtained from the different hemovigilance systems are difficult because (1) the definitions of transfusion complications vary between systems (and sometimes also between reporting facilities from the same system); (2) the denominators necessary for the estimation of the risk of a transfusion-related death are often unavailable or inconsistent between systems; and (3) the criteria used to definitely, probably, or possibly attribute a death to ABT also vary. Thus, for the first 12 years of reporting (1996-2008), 125 deaths were definitely, probably, or possibly attributed to ABT by the United Kingdom SHOT system.[16] Of the 125 deaths, 40 were due to TRALI, 24 to incorrect blood component transfusion (a category that would encompass ABO HTRs), 13 to transfusion-associated (TA)-GVHD, 11 more to HTRs, and 10 to TAS. There was also 1 death from malaria, 3 from variant Creutzfeldt-Jakob disease (vCJD), and 2 from posttransfusion purpura.

Infectious causes of death accounted for 14 (11.2%) of 125 deaths reported to the United Kingdom SHOT program in 1996 to 2008[16] and for 28 (13.2%) of 212 deaths reported to the FDA in 2005 to 2008.[1] Except for the 10 deaths from babesiosis reported to the FDA,[1] the 1 death from malaria, and the 3 deaths from vCJD reported to the United Kingdom SHOT,[16] all other deaths from infectious causes reported to these 2 surveillance systems (28/42 deaths or 66.7%) were due to TAS. Another analysis of 3 FDA databases (Biological Product Deviation Reports and Adverse Event Reporting System in addition to the Fatality Reports)[58] increased the number of deaths from transfusion-transmitted babesiosis in 2005 to 2007 from 5 to 8 and would therefore increase the total for 2005 to 2008 (Fig 2) from 10 to 13. Even when this correction is made, infectious causes of death account for only 31 (14.4%) of 215 transfusion-related fatalities reported to the US FDA in the last 4 years. Thus, underreporting of fatalities aside, deaths from infectious causes have been less than 15% of all reported deaths after the implementation of bacterial detection of platelets.

This low frequency of deaths from infectious causes is partly due to the fact that the numbers shown in Figures 1 to 6 that have been obtained from hemovigilance programs. Although transfusion-transmitted diseases must be reported, such systems are designed to identify acute adverse outcomes of ABT, and they do not capture deaths from chronic infections acquired through an ABT received years before it resulted in the death of the transfusion recipient. The recording by the United Kingdom SHOT system of deaths from transfusion-acquired vCJD is due to the active surveillance efforts made in the United Kingdom to identify cases of transmission of vCJD through ABT. Thus, passive surveillance systems are likely to miss even some acute infections transmitted through ABT, as has been demonstrated for TAS,[59] and was likely the case with some West Nile virus (WNV) infections occurring in New York in the summer of 1999 (when no transfusion-transmitted cases were reported) and with some dengue fever virus (DFV) infections occurring in endemic areas over many decades.

The effectiveness of the current surveillance systems may thus be low, particularly at the point of recognition of events by physicians and their subsequent reporting to transfusion services.[60] Clinicians seeing a patient with DFV infection during outbreaks are unlikely to consider ABT as a possible source of that patient's infection and obtain the critical history of recent transfusions. As a result, the transmission of DFV through ABT had gone undetected until recently.[61,62]

MORTALITY FROM INFECTIOUS COMPLICATIONS OF ABT

Since the mid-1980s, the incidence of HBV, HCV, and HIV infections has significantly declined in blood donors because of better predonation screening criteria and also a decrease in the incidence of these infections in the general population.[27] At the same time, measures introduced in the United States to reduce the risk of TTIs have included HIV-1 antibody testing (introduced in 1985), surrogate marker testing for non-A, non-B hepatitis (1986-87), HTLV antibody testing (1988), HCV antibody testing with first- (1990) or second-generation (1992) tests, HIV-1 p24 antigen testing (1996), testing for HCV (1999) and HIV-1 (2000) viral nucleic acid, detection of bacteria in platelets (2004), and testing for antibody to *Trypanosoma cruzi* (2007). Thanks to all these measures,[27] the estimated risk of transmission of HBV, HCV, HIV, and HTLV infection in the United States[63] is currently approximately 1 per 205 000, 1 per 1 935 000, 1 per 2 135 000, and 1 per 2 993 000 donations.[63-66] Moreover, the window period for

these infections has been reduced and is currently estimated at 9.1 days for HIV, 7.4 days for HCV, and 38 days for HBV.

There have been no reports of fulminant transfusion-transmitted HBV infection in North America and Europe, and only a minority of transfusion recipients survive long enough[25] to develop transfusion-acquired AIDS, cirrhosis or hepatocellular carcinoma due to chronic HBV or HCV infection, adult T-cell leukemia, or HTLV-associated myelopathy. The risk of transmission of HBV infection through ABT is higher than that of HCV or HIV infection, and it will likely remain so even with the impending implementation of testing for HBV nucleic acid that will reduce the 38-day window period by 5 to 8 days.[67] Most adults infected with HBV resolve their infection. There is only a 5% chronic carrier rate in adults, and severe liver disease occurs in 15% to 25% of chronically infected persons several decades later. Immunocompromised patients and infants infected through transfusion may have a higher chronic carrier rate, as well as a higher risk of developing severe disease than the general adult population.[68] Furthermore, despite lack of HBV surface antigen detection in peripheral blood, HBV DNA can persist for decades in the serum and liver of some patients, and the clinical importance of this finding remains to be assessed in long-term studies.[69]

One concern remains, that is, the concern that a benign infection may become a serious pathogen in transfusion recipients who have been rendered immunocompromised by modern medical treatments, especially immunosuppression. These transfusion-transmitted agents include Cytomegalovirus (CMV) and other herpesviruses, human parvovirus B19, and *Babesia* species. In this context, low birth weight neonates and immunocompromised patients are at particular risk for (potentially fatal) transfusion-acquired CMV disease. Transmission of the latter may be prevented by testing donors for CMV antibody and/or removing the mononuclear cells that harbor the CMV virus by WBC reduction. Nonetheless, a small, but real and probably intractable, risk of transmission remains, whether CMV-seronegative or WBC-reduced blood components are used. This contemporary risk is 2% to 4% per transfusion recipient in the setting of bone marrow transplantation.[70,71] Thus, in 502 CMV-seronegative patients enrolled in the study of Bowden et al,[70] there were 10 cases of CMV infection and 6 deaths from CMV disease. Three of these deaths could definitely be attributed to the ABT, as they had occurred in patients developing CMV disease 21 to 100 days posttransplantation.[70]

In 2002, the US mosquito-borne WNV epidemic resulted in 23 confirmed cases of transfusion-transmitted WNV infection with 7 WNV-related deaths.[72] Testing for WNV nucleic acid was introduced in North America in July 2003, but WNV transmissions and deaths have occurred even after the introduction of such testing.[73] In late summer 2002, the risk of transfusion transmission of WNV may have been as high as 1 per 1000 in the most severely affected geographic regions, even though most transmissions resulted in asymptomatic infections.[74] Interestingly, 1 of every 45 blood donations obtained from residents of the Platte River drainage area in Nebraska was reactive.[75] Overall, if 5% of those asymptomatically infected with WNV in 2002 had donated blood, about 380 infectious donations[75] could have been made during the 7-day period of viremia.

Although lacking an intermediate avian host that could facilitate its spread to North America and Europe, DFV is transmitted by mosquitoes that are already present in North America, has a median viremia of 5 days, and causes asymptomatic infection in most cases. Two cases of transfusion transmission have been documented, although more have undoubtedly occurred in endemic areas.[61,62] Thus, DFV may well replicate the 2002 epidemic of transfusion-acquired WNV infection in North America in the future. Other arboviruses may pose a similar threat.[76] Chickungunya virus caused several outbreaks on islands in the Indian Ocean and in India, and in the summer of 2007, 205 cases of infection (imported by a visitor from India) occurred in Italy where mosquitoes capable of transmitting the virus exist.[77]

The number of vCJD cases worldwide has barely exceeded 200, most of which have occurred in the United Kingdom.[78] The vCJD incidence appears to be falling; mathematical projections have suggested an upper limit of around 70 further clinical cases in the United Kingdom,[79] or that 3800 people aged 10 to 30 years (1 per 11 000 in the United Kingdom population) may be incubating the disease.[80] The transmissible spongiform encephalopathies (such as vCJD) may have incubation periods of up to 50 years,[81] with infectious particles (prions) potentially circulating in the peripheral blood for much of the presymptomatic phase of the infection.[82] Thus,

measures to protect the blood supply from the abnormal proteinaceous particles of vCJD are being actively evaluated in the United Kingdom, and implementation of a protective measure(s) is expected in the near future. Possible measures include filtration of blood components through prion-retention filters and/or testing of donor blood for the abnormally conformed prion protein by such methods as protein misfolding cyclic amplification.[82] Five probable cases of transfusion transmission of vCJD have been reported from the United Kingdom in patients who had received blood from asymptomatic donors who later developed vCJD.[83]

Donor screening for protozoal transfusion-transmitted diseases began in the United States in 2007, with the introduction of testing for *Trypanosoma cruzi*, although various testing approaches had already been used in Europe. Between 1963 and 1999, 93 cases of transfusion-acquired malaria were reported in the United States of whom 10 (11%) died.[84] Three cases were reported in Canada between 1994 and 1999,[85] but in endemic countries, the risk of transmission can be as high as 50 cases per million RBC units transfused.[86] More than 3000 cases of transfusion-transmitted malaria have occurred worldwide,[87] although the reported cases may represent less than 50% of the actual cases.[88] Furthermore, more than 70 cases of transfusion-transmitted babesiosis—including many fatalities—have been reported from the United States.[58] This figure captures splenectomized and immunocompromised recipients at risk for severe disease and is likely an underestimate.[89] A study in an endemic area (Connecticut) estimated the risk of transfusion transmission to be 1 per 601 transfused RBCs.[90]

Other potentially fatal TTIs include leishmaniasis[91] and Chagas' disease.[92-95] Any agent that even transiently traverses the human circulation during an asymptomatic phase of infection may prove transfusion transmissible. Sixty-eight potentially or known transfusion-transmitted agents were prioritized by an AABB Task Force in a special report published in July 2009.[29]

Emerging Transfusion-Transmitted Infections

The most dramatic example of an emerging infection is the appearance of a completely new infection, as was the case with the HIV infection. The latter probably occurred as a result of a cross-species transmission of simian immunodeficiency viruses from monkeys to great apes and then to humans.[96] The original transmission probably occurred as a result of the preparation of bushmeat derived from apes. Another cause of the emergence of novel agents is the expansion of existing infections into a larger geographic area; a striking example of such expansion was the recent appearance of WNV in the Americas.[97] In a similar manner, DFV and Chikungunya virus may very well be expanding their current geographic regions.[98-100]

Provided that an agent can survive in blood components and can be transmitted by the intravenous route, any infection with an asymptomatic blood-borne phase has the potential for transmission by ABT. This possibility exists, whether the infectious phase is prolonged (as is the case with HIV, HBV, or HCV infection) or short (as is the case with WNV or DFV infection). The frequency with which an infection is transmitted to a transfusion recipient depends on the length of the asymptomatic blood-borne phase, how often blood is donated during this period, and the immune status of the recipient population.[29]

The AABB Task Force[29] recently prioritized 68 potentially or known transfusion-transmitted agents based on both the existing scientific and epidemiologic evidence of their transmissibility through ABT and their potential for severe clinical outcomes that could result in public attention and concern. Four priority categories were assigned to convey a particular agent's significance as follows: white, yellow, orange, and red. Agents included in the red category were the vCJD prions, DFV, and *Babesia* species. Agents included in the orange category were *Leishmania* species, *Plasmodium* species, *Trypanosoma cruzi*, Chickungunya virus, and St Louis encephalitis virus (SLEV).[29] With the exception of the last 2 agents (Chickungunya virus and SLEV), all other agents prioritized as red or orange have been shown to be transfusion transmitted.

Because the focus of this report was the United States, protozoa that represent major transfusion risks in developing countries (*Plasmodium* species and *Trypanosoma cruzi*) were placed in the same category as SLEV—for which there is no evidence of transmission by transfusion but which is endemic in the United States. For both Chickungunya virus and SLEV, the Task Force's concern was that these agents have the potential to replicate the 2002 WNV US experience in the future. Concerning the United States, the Task Force judged the medical and scientific evidence

for transmission of *Babesia* species to be moderate to high, whereas the evidence for DFV and vCJD prions was judged to be low. Nonetheless, concerning the effect in developing countries, the medical and scientific evidence for transmission of DFV was judged to be moderate.[29]

Three transfusion-transmitted agents have emerged in the last 30 years as follows: HIV, vCJD prions, and WNV. Therefore, it is not prudence but common sense to assume that what happened in the past can (or will) happen again in the future. The worst that can happen is that an HIV-like pathogen with a long incubation period could emerge that—owing to its long asymptomatic blood-borne phase—could accumulate to a significant extent in the blood donor population before it becomes recognized, thereby almost reaching the prevalence of the HIV infection in the US blood donor population before testing for HIV antibody was introduced. In 1984—the year before testing of US blood donors for HIV infection commenced—the prevalence of HIV infection in donors exceeded 1 per 1000.[101] Because of the surveillance systems put in place after the 1980s epidemic of transfusion-acquired HIV infection, it is unlikely that a new viral agent causing chronic infection could go undetected for as long as HIV went undetected, and therefore, infection with a new viral agent would be most unlikely to reach a prevalence of 1 per 1000 US blood donors.

Although a future HIV-like agent would certainly be detected much faster than HIV was recognized, it is still possible that—before measures are implemented to interrupt its transmission through ABT—the future HIV-like agent could reach a prevalence as high as 10 times less than the 1984 HIV prevalence. Thus, worst case scenarios of all strategies to further reduce ABT-related mortality should consistently model the possibility of an HIV-like pathogen reaching a prevalence of 1 per 10 000 US blood donors before measures are introduced to interrupt its transmission through transfusion.[102] Importantly, we cannot exclude the possibility that the accumulation of such a pathogen in the US blood donor population may have already started occurring.

Similarly, a WNV-like agent can change its geographic distribution and emerge in the United States as a transfusion-transmitted pathogen, causing 380 transmissions through ABT in its first seasonal epidemic,[75] as was the case with WNV in the summer of 2002.[102] Both an HIV-like and a WNV-like future pathogen could be transmitted equally effectively through transfusion of RBCs, platelets, or plasma. Thus, the risk of contracting a TTI from a transfusion of n units (or from exposure to n donors) would equal $1 - (1 - p)^n$, where p is the per-unit probability of transmission of the emerging TTI. Because transfusion risks are very low (eg, 1 per 10 000 in the case of a future HIV-like agent), $1 - (1 - p)^n$ approximates p times n, and the per-recipient risk can be calculated by multiplying the per-unit risk by the number of donors to whom a recipient is exposed.

Transfusion-Associated Sepsis

Before the introduction of bacterial detection of single-donor (apheresis) platelets in the United States in March 2004, TAS ranked third among the causes of TA fatalities reported to the FDA. Since then, the number of reported TAS deaths has been reduced to less than half (Fig 4), yet TAS still ranks third among the causes of TA fatalities (Fig 2). Before 2004, estimates of the incidence of TAS varied widely, from approximately 1 per 3000 transfused platelet pools[17,47] to 1 per 100 000 transfusions.[103,104] Actual bacterial contamination rates of blood components were substantially higher.

The data compiled by McDonald and Blajchman[9] from 7 studies of single-donor and 12 studies of pooled whole blood–derived platelets showed contamination rates of 0.09% (31/35 122) and 0.43% (376/87 922), respectively. This (nearly 5-fold) difference was presumably due to the number of venipunctures (1 vs 4-6) involved in the collection of single-donor vs pooled whole blood–derived platelets. In 5 reviewed studies, the RBC contamination rate was 0.1% (60/61 136),[9] probably because the 4°C storage temperature of RBCs inhibits bacterial growth during storage. Given that skin bacteria are the major sources of contamination, the difference between measured contamination rates in stored components and septic reactions in transfused patients likely can be explained by low-level contamination that does not evoke a clinical response, concomitant antibiotic therapy that blunts a clinical response, and/or failure to (correctly) attribute sepsis to the platelet transfusion in patients with neutropenia or fever.

Of the organisms that caused 16 fatalities from contaminated platelet transfusions in the United States,[104] France,[103] and the United Kingdom,[15]

37% (6 cases) were Gram-positive and 63% (10) were Gram-negative.[9] Of the organisms that caused all 72 episodes of TAS,[15,103,104] however, 68% were Gram-positive and 32% were Gram-negative. The most frequently implicated organisms were *Staphylococcus epidermidis*, *Escherichia coli*, *Staphylococcus aureus*, and *Bacillus cereus*.[9] Of the organisms that caused 7 fatalities from contaminated RBC transfusions,[15,103,104] 6 were Gram-negative and 1 was Gram-positive.[9] Overall, platelets were responsible for 70% of the fatalities and RBCs for 30%.[9,21] At the 22°C storage temperature of platelets, a wide range of bacteria are capable of proliferation to levels of 10^6 to 10^{11} colony-forming units/mL,[105,106] and with growth to these levels, contaminated blood component units can lead to significant morbidity and mortality.

In the SHOT reports,[16] of the cases where the age of the platelet component was known, 75% of episodes of TAS occurred when the product was 4 to 5 days old. Reducing the allowable storage time to 3 days would prevent such episodes but would very likely result in supply problems. Moreover, 50% of the SHOT fatalities were due to platelet components aged 2 to 3 days. Reducing the storage time would not prevent fatal cases such as these. In some European centers, the introduction of bacterial detection in platelets using automated culture systems enabled the storage time to be extended to 7 days. The US FDA had allowed the storage time of platelets to be extended to 7 days in 1983, but it soon returned the shelf life back to 5 days because of a reported increased incidence of fatal TAS episodes.[107] Recently, experimental protocols considering extension of the storage time of platelets to 7 days (after the introduction of automated bacterial culture systems) were halted in the United States because of an increased incidence of TAS.[108]

The same relationship between prolonged storage and increased risk of TAS has been reported for RBCs contaminated with *Yersinia enterocolitica*. Yersinia grows well at 4°C, uses the citrate of the preservative solution as a source of energy, and, owing to its lack of siderophores, requires iron for optimum growth. Stored RBCs thus provide an ideal growth medium for this microorganism. In almost all serious reactions to RBCs containing *Y enterocolitica*, the RBCs had been stored for more than 3 weeks.[109]

Before or around 2004, improved donor selection (intended to exclude prospective donors with bacteremia), improved donor arm disinfection, diversion of the initial flow of donor blood (presumed to contain the skin contaminants) from the collection bag into a pouch, overnight hold of the collected whole blood, and/or WBC reduction had reduced, but not eliminated, the risk of bacterial contamination of blood components.[9] In 2004, the AABB required measures to limit and detect bacterial contamination in all platelet components. At that time, suitable automated bacterial culture systems were available only for apheresis platelets in the United States but have since become available to be used for pooled whole blood–derived platelets as well.

Because of the risk of sampling error, even the most sensitive methods currently available for automated bacterial culture testing have a clinical sensitivity of less than 50%.[110,111] Although these bacterial detection systems have excellent analytical sensitivity, owing to the exceedingly low starting concentration of bacteria in platelet components, it is possible to submit for culture such a small volume (<10 mL) from a platelet product that it may contain no bacteria at all. In 2004 to 2006, the American Red Cross (ARC) performed bacterial culture testing on 1 million single-donor platelet donations.[112] Of these, 186 (1 in 5400) had confirmed positive culture results, and transfusion of all but 1 of the associated 293 components was prevented. During this period, however, 20 episodes of TAS secondary to (screened) single-donor platelets were reported, including 3 fatalities (1 per 498 711 distributed components). Most TAS episodes were associated with components stored for 5 days.[112] Comparison of the risk of TAS and TAS-related death from single-donor platelets before and after implementation of bacterial culture testing of single-donor platelets indicated a 50% decrease in reported events (1 per 75 000 vs 1 per 40 000) and fatalities (1 per 500 000 vs 1 per 240 000 components).

The clinical implications of this declining trend (P = .11) were unclear. It could reflect poor sensitivity of the automated bacterial culture systems,[110,111] increased recognition and reporting of TAS over time, or both. Most likely, it meant that the risk of TAS before March 2004 was greater than generally appreciated at that time and also that a significant risk remains despite the implementation of bacterial culture systems.

Reactions and fatalities after the introduction of bacterial culture testing have also been reported from other blood systems and with both available culture systems.[113-116] In Canada, there were 2 TAS episodes and 1 fatality among recipients of 82 004 cultured single-donor platelets.[114]

After reporting the 2004-2006 results for single-donor platelets,[112] the ARC in 2007 to 2008 conducted a follow-up study[117] after the optimization of the collection conditions and the doubling (from 4 mL to 8 mL) of the volume of the sample submitted for culture. The reported rate of events (1 per 87 000) did not differ significantly from that in the previous period (1 per 75 000). Interestingly, 9 culture-negative single-donor components were passively reported to the ARC as having caused TAS during this latter period. Another estimate of the magnitude of the risk was reported from the Johns Hopkins Hospital that maintains active surveillance for TAS. One per 50 000 culture-negative single-donor platelet components caused TAS between March 1, 2004, and August 31, 2007.[118] Only 1 episode of TAS occurred in this study, however, which predated the process improvements implemented by the ARC[117] in 2007 to 2008.

The studies that compared the frequency of bacterial contamination between pooled whole blood–derived and single-donor platelets in settings that had implemented bacterial culture testing of both components simultaneously were subjected to a meta-analysis.[102] Across 3 studies conducted in the United States,[119-121] pools of 5 whole blood–derived platelet concentrates had a 5.6-fold higher frequency of bacterial contamination than single-donor platelets (summary odds ratio [OR], 5.58; 95% confidence interval [CI], 2.60-11.98; $P < .05$). In contrast, across 4 studies conducted in Europe,[110,115,122,123] there was no difference in the risk of bacterial contamination between pooled whole blood–derived and single-donor platelets (summary OR, 0.99; 95% CI, 0.63-1.57; $P > .05$). Both subsets of studies were highly homogeneous statistically ($P > .90$ for the Q test statistic), despite the fact that the processes of component collection and preparation, as well as the culture conditions, sampling volumes, use of anaerobic bottles, and the criteria for determining true-positive results differed across the studies.

Whether the difference between the findings of the 2 analyses was due to the different method of platelet preparation (platelet-rich plasma platelets in the United States vs buffy coat platelets in Europe) or factors associated with the method of platelet preparation (eg, overnight hold of the collected whole blood in Europe) could not be determined by the meta-analysis because the method of platelet preparation overlapped with all the other sources of heterogeneity.[102] A theoretical justification for a lower bacterial risk associated with buffy coat platelets has been advanced.[124] A synthesis of all 7 studies[110,115,119-123] could not be undertaken owing to significant statistical ($P < .005$ for the Q test statistic) and medical heterogeneity.[102] The result of the meta-analysis concerning the difference in risk between pooled whole blood–derived and single-donor platelets in the United States was what would have been expected from the difference in the number of venipunctures done.[47,48]

Figure 7 combines various published estimates[9,17,47,55,110,111] and the findings of the meta-analysis[102] to derive an estimate[102] of the risk of TAS associated with pooled whole blood–derived vs single-donor platelets manufactured in the United States under a best-case scenario (ie, assuming that all pooled whole blood–derived platelets distributed in the United States—12.5% of therapeutic platelet doses currently[56]—will soon be prepooled and cultured).

MORTALITY FROM NONINFECTIOUS COMPLICATIONS OF ABT

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury has emerged as the leading cause of transfusion-related mortality in the United States (Figs 1 and 2).[1] Transfusion-related acute lung injury is a new ALI occurring within 6 hours after a transfusion, with a clear temporal relationship to the transfusion, in patients without risk factors for ALI other than transfusion.[10,125] Thus, the Canadian Consensus Conference definition of TRALI[11] was based on the American-European Consensus conference definition of ALI[50] and a temporal relationship to the transfusion. The definition of ALI requires that the possibility of circulatory overload (ie, left atrial hypertension) be ruled out. Once circulatory overload has been excluded, however, the consensus definition of TRALI[11] allows for a diagnosis of "possible" TRALI to be made in cases in which patients have other risk factors for ALI temporally

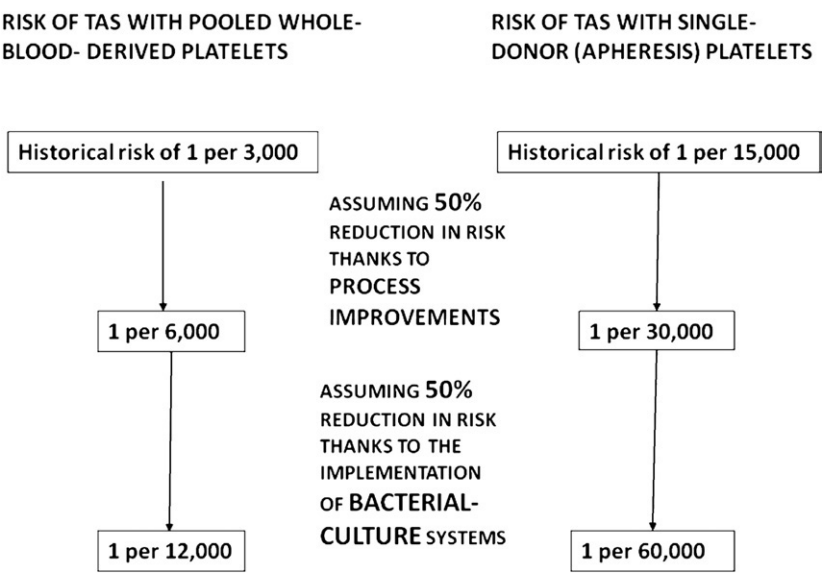

Fig 7. Estimation of the risk of TAS from platelet transfusions in the United States today.[102] The depicted historical risk represents empirical data from settings[17,47] in which all febrile reactions to platelets were monitored and cultured.[102] The estimates of current risk are based on the assumption that all whole blood–derived platelets distributed in the United States will soon be prestorage-pooled and cultured. For estimates of risk in the contemporary (October 2009) setting—when surrogate methods (rather than bacterial culture) are usually used to screen pooled whole blood–derived platelets for bacteria—see Vamvakas.[102]

related to the transfusion.[11] The latter include sepsis, aspiration, pneumonia, toxic inhalation, lung contusion, near drowning, multiple trauma, burn injury, acute pancreatitis, cardiopulmonary bypass, and drug overdose.

Transfusion-related acute lung injury has a clinical presentation mirroring ARDS[50-52] after ABT.[10,11,125] In contrast to ARDS, however, patients with TRALI typically recover with resolution of their pulmonary infiltrates within 96 hours, and the case fatality ratio is only 5% to 10%.[2] To avoid (1) spurious associations between TRALI and transfusions of blood components collected from female donors or donors with circulating WBC antibodies, or (2) a diagnostic suspicion bias for TRALI when WBC-antibody tests on female donors show WBC antibodies in the plasma of a donor(s) of a component(s) given to a patient with ALI in the presence of other risk factors for ALI (Fig 8), the diagnosis of TRALI is to be made solely on the basis of the clinical presentation, regardless of what laboratory tests follow and their results.[11]

The incidence of TRALI is unknown because a standardized definition[10,11] has not been available until relatively recently. Early reports quoted an incidence of 1 per 5000 transfused blood components,[2] with subsequent reports ranging from 1 per 432 platelet pools[42] to 1 per 557 000 RBCs.[15] TRALI has been reported with the use of all types of blood components. Most blood components implicated in published case-reports and small case-series have contained more than 50 mL of plasma, and FFP has been the most frequently implicated component.[2,126,127] However, TRALI also occurs with whole-blood-derived platelets[128-132] and with components containing as little as 10 mL of plasma.[133] Importantly, not all the pre-2004 literature had indicated that FFP or components containing large volumes of plasma are the principal culprits.[17,42]

Theories of TRALI pathogenesis. Transfusion-related acute lung injury can be due to WBC antibodies, soluble biologic response mediators accumulating during the storage of cellular blood components, or other still unidentified agents contained in transfused blood components.[10] The WBC antibodies in transfused plasma can be directed against the recipient's WBC antigens and interact with antigens on the patient's WBCs in the microcirculation of the lungs.[2,5] Neutrophil-specific antibodies, especially antibody to the human neutrophil antigen-3a, appear to be relevant.[134-137] Nonetheless, the presence of a WBC antibody in a donor does not predict the occurrence of TRALI in

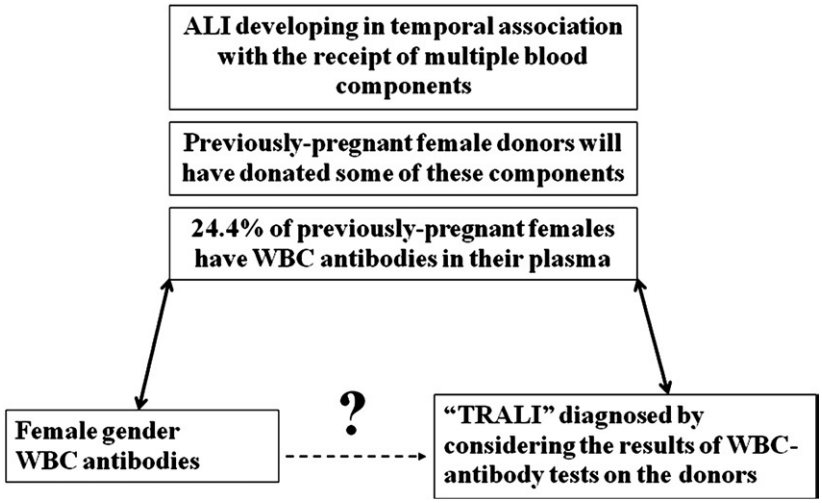

Fig 8. Effect of taking into account, for the diagnosis of TRALI, the laboratory results of donors tested for WBC antibodies. Because HLA antibodies are present in the serum of 24.4% of women who have previously been pregnant,[13] and multitransfused patients are likely to have received some blood components from previously pregnant female donors, such recipients will be likely found to have received components from donors whose plasma contains WBC antibodies, regardless of whether TRALI is (or is not) present. Therefore, female donors and WBC antibodies are likely to be spuriously associated with TRALI when the results of such laboratory tests are considered in making the diagnosis. Such spurious associations may have been the origin of TRALI in some of the cases included in series compiled by blood suppliers on the basis of passive surveillance reports received from hospitals when the recipient's serum was no longer obtainable. For these reasons, the consensus criteria[11] require that the diagnosis of TRALI be made clinically, without considering the results of laboratory tests. Provided that the diagnosis of TRALI has been made in this manner,[11] the further designation of alloimmune TRALI should be reserved for cases of proven WBC incompatibility between an implicated donor and the relevant cognate recipient WBC antigen. In the case of common WBC antigens (and antibodies), even WBC incompatibility between an implicated donor(s) and the recipient can occur by chance. Thus, although such WBC incompatibility strengthens the belief in the correctness of the diagnosis in the appropriate clinical setting, it should not be used as the basis for the diagnosis.

the recipient.[138] Most WBC antibody infusions do not cause TRALI, making it possible that alloantibodies—albeit present in most TRALI cases—could be a surrogate for another etiologic factor. The clinical evidence that relates TRALI to WBC antibodies can indeed be explained by such spurious associations as those shown in Figure 8, and the link between TRALI and WBC antibodies remains circumstantial.[139]

In support of the antibody hypothesis of TRALI pathogenesis, the infusion of WBC antibodies in an ex vivo animal model precipitated TRALI in the absence of other factors precipitating TRALI.[140] Most donors implicated in TRALI have been multiparous women and 14 (87.5%) of 16 TRALI cases in one series[126] demonstrated WBC antigen/WBC antibody correlation. Eder et al[127] reviewed 550 reports of suspected TRALI, including 72 fatalities, submitted to the ARC in 2003 to 2005. Thirty-eight fatalities were categorized as "probable" TRALI and 24 (63%) of them had occurred after FFP transfusion. A female, WBC antibody-positive donor was involved in 27 (71%) of all TRALI fatalities, and in 18 (75%) of 24 deaths implicating FFP transfusion. Data from the United Kingdom SHOT system[141] reported donor WBC antibodies recognizing a cognate WBC antigen in the transfusion recipient in 62 (65%) of 96 completely investigated TRALI cases. Three clinical studies[142-144] have demonstrated an association between female FFP and impaired pulmonary function/hypoxia, albeit not TRALI.

More specifically, a crossover RCT in 105 ICU patients showed impaired pulmonary function occurring more frequently in patients receiving FFP from multiparous women vs controls.[142] After the conversion to male-only FFP in the United Kingdom, a before and after observational study in multitranfused patients undergoing abdominal aortic aneurysm repair demonstrated a reduced risk of hypoxia when only male-only FFP was administered.[143] A prospective observational study comparing 55 recipients of male-only FFP with 27 recipients of "mixed" (ie, both male and female) FFP in Japan[144] observed development of pulmonary distress—defined as a Pao_2/fraction of

inspired oxygen ratio of less than 300—in 19 subjects within 6 hours of the transfusion (5 patients with possible TRALI, 7 with TACO, and 7 with no apparent pulmonary edema). The receipt of male-only FFP was associated with a reduction ($P = .02$) in the risk of pulmonary distress. However, 2 subjects (3.6%) receiving male-only FFP vs 3 patients (11.1%) receiving "mixed" FFP developed possible TRALI ($P = .18$).[144]

The WBC antibodies were associated with the development of TRALI in the univariate—albeit not the multivariate—analyses of the hitherto reported prospective observational studies that have included consecutive transfused patients.[43,144] These studies[43,144] therefore suggest that male-only FFP will be advantageous for posttransfusion pulmonary function, although other patient-related factors such as sepsis and fluid balance as opposed to the receipt of female FFP are the primary determinants of ALI in multiply-transfused patients.

In fact, alternatively (or additionally) to WBC antibodies, the 2-hit model proposed by Silliman et al[46] may explain the development of TRALI in transfusion recipients with various preexisting risk factors for ALI. Initial insult to the vascular endothelium (due to infection, surgery, trauma, or massive transfusion) attracts and primes neutrophils that adhere to the endothelium. A second "hit" is then mediated by biologic response modifiers contained in transfused plasma (eg, lipid-priming molecules found in the plasma supernatant of stored [as opposed to fresh] RBCs and platelets, cytokines, CD40 ligand, and/or WBC antibodies). These molecules activate the sequestered neutrophils to release oxidases and proteases that damage the endothelium and produce capillary leak and ALI. A rat model demonstrated that TRALI is the result of 2 events; the first is the clinical condition of the patient and the second consists of antibodies that prime neutrophils and/or plasma from stored blood.[45] The findings of the completed prospective observational studies[43,144] (which underscored the role of patient-related factors) are also consistent with this 2-hit (or bioactive-lipid/neutrophil-priming) hypothesis.

If the diagnostic criteria for TRALI required that all alternative risk factors for ALI had to be excluded before a diagnosis of TRALI could be made, virtually no cases of TRALI mediated by such a 2-hit mechanism would be diagnosed as TRALI. Such an approach to the diagnosis may explain the very high prevalence of WBC antibodies (as well as the female sex of the donors of the implicated blood components[13]; Fig 8) in the pre-2004 literature on TRALI. Accordingly, the Canadian consensus criteria[11] permit the diagnosis of "possible" TRALI in patients who have other risk factors for ALI yet the clinical setting makes the diagnosis of TRALI likely. If the consensus criteria[11] are not adhered to, however, many clinicians and laboratorians will be dissuaded from making a diagnosis of TRALI either in the absence of donor WBC antibodies or in the presence of alternate risk factors for ALI. It is hard to determine what impact these 2 diagnostic biases may have had on the collection of case reports and small case series that comprise most of the pre-2004 literature on TRALI.

Approaches to TRALI prevention. The Canadian Consensus Panel[11] noted that the 2 hypotheses for the cause of TRALI suggest different strategies for prevention. The antibody hypothesis[2,5] supports the exclusion of plasma from donors with pathogenic antibodies, whereas the bioactive-lipid/neutrophil-priming hypothesis[44,45] supports a reduction in the length of storage or the washing of cellular blood components regardless of donor characteristics. The Consensus Panel[11] noted that both preventive strategies have the potential to reduce the blood supply by excluding safe donors (in accordance with the antibody hypothesis of TRALI pathogenesis) or safe products (in accordance with the bioactive-lipid/neutrophil-priming hypothesis). Hitherto, no country appears to have implemented a reduction in the length of storage or the washing of cellular blood components to reduce the risk of TRALI.[145] Following the United Kingdom, several European countries as well as the United States and Canada[146] converted to male-only FFP as a risk reduction strategy. These countries, however, have yet to convert to a single-donor platelet supply collected solely from male donors (or female donors without a history of pregnancy or shown not to have WBC antibodies).[147]

The US Leukocyte Antibody Prevalence Study enrolled 5700 female donors, 1100 transfused male donors, and 1100 nontransfused male donors, and it used a validated questionnaire to elicit a history of all pregnancies, including miscarriages and terminations.[13] The HLA antibodies were detected in 24.4% of females with a history of pregnancy, 1.7% of females who had never been pregnant, 1.0% of

nontransfused males, and 1.7% of transfused males. Females who had never been pregnant, nontransfused males, and transfused males had the same prevalence of HLA antibodies. Transfusion alone did not result in increased prevalence of HLA antibodies. However, the time since the last transfusion in the donors enrolled in the Leukocyte Antibody Prevalence Study was very long (a median of 22 years). The study did not evaluate recently transfused donors who might have circulating HLA antibodies even if such antibodies fall to undetectable levels in a matter of months after ABT.[147] The reason for the 1.0% and 1.7%, respectively, prevalence of HLA antibodies in nontransfused males and never-pregnant females is uncertain. They could represent false-positive results, antibodies cross-reacting with bacterial antigens, or immunization associated with vaccination.[147]

Impact of the Canadian 2004 Consensus Criteria on diagnoses of TRALI. The United Kingdom SHOT system has not been using the Canadian consensus criteria[11] for diagnosing TRALI, thereby, perhaps excluding cases in which WBC antibodies are not demonstrated or relegating them to a "possible TRALI" category.[148] Similarly, 2 years after the publication of the consensus definition,[11] 45% to 66% of US hospitals were basing their diagnoses of TRALI on a combination of clinical and serologic findings.[149] Workups regularly included HLA class I and II antibodies and sometimes neutrophil antibodies as well. Which donors were screened for WBC antibodies often hinged on a donor's sex, and policies bearing on the diagnosis of TRALI were decided on a case-by-case basis.

Figure 8 shows how this (historic) approach to the diagnosis would have produced associations of female sex and WBC antibodies with clinical diagnoses of TRALI as well as reports of TRALI in the pre-2004 literature. Even in the recent literature, however, the Canadian consensus definition has not been consistently adhered to. For example, in a recent RCT[150] of the efficacy of WBC-reduced blood components in preventing TRALI, none of the diagnoses of TRALI assigned in either arm of the trial pertained to ALI occurring within 6 hours of ABT.[151] Because ALI is very common in critically ill multitransfused patients, many cases of ALI can be misdiagnosed as "TRALI" because of a temporal association with the transfusion. The demonstration of WBC incompatibility between an implicated donor and the recipient (as opposed to the mere presence of WBC antibodies in an implicated donor's serum) strengthens the evidence that a particular case of ALI (in which all consensus criteria[11] have been met and the diagnosis of TRALI has been made before the laboratory workup) represents TRALI. However, whether TRALI is mediated by its own pathogenetic mechanisms (distinct from the generic mechanisms of ALI) remains unknown.[152]

Even when the Canadian consensus criteria[11] are adhered to, a diagnosis of TRALI represents best clinical judgment rather than a firm diagnosis buttressed by a pathognomonic diagnostic test. This is because the criteria[11] are broad and subjective, and they do not specify how the principal differential diagnosis of TACO is to be made from TRALI in routine clinical settings. The subjective nature of the diagnosis is highlighted when clinically and serologically "documented" cases of TRALI not meeting the consensus definition are reported.[153]

Forty-nine cases of TRALI were diagnosed in the Netherlands between January 2005 and July 2007, by both adhering strictly to the Canadian consensus criteria and performing a complete TRALI workup (which included both tests for WBC antibodies in the sera of all implicated donors and a WBC incompatibility test between the implicated donors and the recipient).[148] Of 49 patients, 44 underwent such complete laboratory workups the purpose of which was not to make the diagnosis of TRALI per se but to identify the subcategory of cases of "alloimmune" TRALI. In 36 cases (73.5%), at least one implicated donor had WBC antibodies. In 21 cases (43%), serologic incompatibility was demonstrated between at least one donor and the recipient (ie, the donor's antibody was directed against a cognate WBC antigen of the recipient).

These cases of alloimmune TRALI demonstrated more severe morbidity (compared with the remaining 28 cases), although mortality was not increased. Two hundred fifty-nine components (129 RBCs, 66 platelet pools, and 64 U of FFP) had been administered to these 49 multiply-transfused patients. When the analysis was limited to the 21 cases of alloimmune TRALI—which involved 31 donors with demonstrated serologic incompatibility between donor and recipient—25 (81%) donors were female and 6 (19%) were male. Of the 31 implicated components, 14 (45%) were FFP, 14

(45%) were RBCs, and 3 (10%) were platelet pools. The Netherlands converted to male-only FFP in July 2007 when the study was terminated. Had male-only FFP been used during the 30 months of the study, 12 (24.5%) of the 49 cases could have been prevented; up to 3 (30%) of the 10 TRALI deaths could potentially have been prevented as well. Of the 10 patients who died of TRALI, 7 had received only RBCs.[148]

Also adhering strictly to the Canadian consensus criteria,[11] the Canadian Transfusion-Transmitted Injuries Surveillance System reported on 105 TRALI cases that had occurred in 2004 to 2005.[41] Of 372 respiratory complications of ABT reported to the Transfusion-Transmitted Injuries Surveillance System, 257 were deemed to represent TACO, 8 TA dyspnea, 2 possible TRALI, and 105 probable TRALI. Of the 105 cases of probable TRALI, 57.1% were associated with RBCs, 21.0% with FFP, 7.6% with pooled whole blood–derived platelets, and 3.8% with single-donor platelets. There were 5 deaths (case fatality ratio of 4.8%): 4 deaths were attributed to transfusion of RBCs and 1 to transfusion of FFP.

The benefit from converting to male-only FFP[41,148] will thus likely be significantly smaller than that predicted from the United Kingdom SHOT system reports[144,146] (Fig 6) or earlier case series.[126] Although consensus about the appropriateness of converting to male-only FFP has not been achieved[154] and not all studies have shown a reduction in the risk of TRALI through avoidance of female donors,[155,156] most of the adduced evidence does support the thesis that this measure will enhance blood safety.

Gajic et al[43] presented a prospective cohort study of 901 patients sequentially admitted to the medical ICU and evaluated for TRALI based on the Canadian consensus criteria[11] that capture both suspected TRALI cases (with no identifiable preexisting risk factor for ALI) and possible TRALI cases (where at least one alternate risk factor for ALI is present). Seventy-four patients developed TRALI. Of these, 62% had another risk factor for ALI, highlighting the interaction between ABT, patient factors, and development of TRALI. This finding underscores the risk of ARDS (diagnosed as either ALI or TRALI) in critically ill patients with preexisting risk factors of ALI who receive transfusion of even a single-unit of blood.[157] Gajic et al[43] compared the 74 TRALI cases to 74 controls drawn from among the patients who did not develop worsening respiratory status within 24 hours of the ABT. The cases received more units from female donors and donors with more pregnancies, as well as more FFP and FFP from female donors with more pregnancies. In contrast, the number of RBC transfusions did not differ between the cases and controls. Both WBC antibodies and bioactive lipids accumulating during storage were higher in the components received by the cases than the controls.

Thus, Gajic et al[43] concluded that, although sepsis was the risk factor most commonly associated with the 74 diagnoses of ALI in this population of critically ill patients,[152] modifiable transfusion factors (ie, donor sex, parity, and WBC alloimmunization) were also associated with TRALI, indicating opportunities for prevention. The WBC antibodies were not associated with TRALI in the multivariate analysis that included the various patient-related risk factors for ALI, yet the most straightforward opportunity for TRALI prevention would be the exclusion of female donors from making donations of FFP. The magnitude of the benefit derived from such a conversion to male-only FFP remains to be determined, but an improvement in blood safety even as small as that suggested by the Dutch data (ie, prevention of 25% of the overall TRALI cases and up to 30% of the overall TRALI deaths)[148] would make the conversion to male-only FFP a worthwhile blood safety measure.

Hemolytic Transfusion Reactions

In HTRs, the transfused donor RBCs are attacked by the recipient's "naturally occurring" antibodies to ABO antigens, and/or antibodies to other RBC antigens, produced after immunization through a previous transfusion or pregnancy. An acute HTR occurs within 24 hours of the ABT, although—in the case of an ABO-incompatible transfusion—it usually begins during the transfusion. A delayed HTR (DHTR) begins after there has been an anamnestic (secondary) immune response to a donor RBC antigen to which the recipient has been alloimmunized by a previous transfusion or pregnancy. From 19.5% to 48.6% of clinically significant RBC alloantibodies to non-ABO antigens disappear over time, predisposing a transfusion recipient to the development of DHTR.[158] It is very rare for a DHTR to cause death, although deaths have been reported.[4,159] The outcome of an

immediate HTR depends on the potency of the (usually ABO) recipient antibody and the volume of blood transfused; infusion rate may also be a factor. Most fatalities have been associated with transfusions of 200 mL or more, and mortality approaches 44% for transfusions exceeding 1000 mL.[4,18]

Of 44 fatalities reported to the FDA because of HTR in 1976 to 1978, 38 were due to ABO incompatibility.[18] The commonest cause of HTR was the failure to identify the intended recipient correctly, and most such incorrect blood component transfusions had occurred in the operating room. Of the deaths reported to the FDA (1976-1985),[4] 158 were due to acute HTRs (131 to ABO incompatibility) and 26 to delayed HTRs (mostly due to c and Jk^a antibodies). If all these deaths were attributed to the ABT, mortality from HTRs would approximate 1 per 250 000 RBC units transfused during the decade 1976 to 1985.

A 10-year (1990-1999) study in New York State documented incorrect blood component transfusion in 1 per 19 000 transfused RBC units, ABO incompatible transfusion in 1 per 38 000, and acute HTR (or laboratory evidence of hemolysis) in 1 per 76 000. Five deaths were reported (case fatality ratio of 2%), resulting in a mortality from acute HTR of 1 per 1.8 million transfused RBC units.[160] This is identical to the figure calculated from French hemovigilance data[14] (1 per 1.8 million transfused RBCs; 95% CI, 1 per 5 million to 1 per 773 000) and similar to the figure of 1 per 1.4 million components issued for transfusion obtained from the SHOT system.[15]

Deaths from ABO HTRs. Proper identification of the transfusion recipient (at the time of transfusion) and of the pretransfusion blood specimen (at the time of specimen collection) are critical for the prevention of ABO HTRs. It is human error that causes transfusion of the wrong unit or miscollection (or mislabeling) of the pretransfusion specimen. Therefore, administrative systems have been developed to analyze errors and prevent their future recurrence.[161] Moreover, because proper identification of the transfusion recipient is crucial, barrier systems intended to physically prevent the transfusion of blood without correct identification of the patient have been devised. These include a plastic lock that must be unlocked by the entry of the correct identification code,[162] use of a special wristband for identification of transfusion recipients,[163,164] multiple barcodes (on patient wristbands, blood sample tubes, blood component bags, and nurses' identification badges) along with point-of-transfusion reading devices to verify identity,[165,166] as well as other similar approaches.[167,168] These tools require investment in information technology, but they can be integrated with other systems such as medication administration. To guard against miscollection (or mislabeling) of the pretransfusion specimen, some US transfusion services require verification of the recipient's ABO group by the collection of 2 independent pretransfusion samples.[169]

Figure 9 shows a reduction in these avoidable deaths from ABO HTRs reported to the US FDA between 1976 to 1985 and 2005 to 2008. The recent decrease in deaths[1] was temporally associated with the February 2004 FDA requirement that machine-readable information be included on blood container labels by April 2006.[170] A similar reduction in ABO-related fatalities was recently recorded by the United Kingdom SHOT system.[16]

Deaths from non-ABO HTRs. Despite the reduction in ABO fatalities, the mean annual number of all deaths from acute HTRs has remained stable between 1976 to 1985 (15.8/y) and 2005 to 2008 (14.0/y) (Fig 9). This is because reported fatalities due to acute HTRs secondary to non-ABO antibodies have increased in recent years.[1] The increasing number of such reports to the FDA probably reflects improved awareness of the potential for non-ABO HTRs to cause death. In 2005 to 2008, non-ABO antibodies were implicated in 60.7% of all fatal HTRs.[1] Implicated RBC antibodies included Jk^b, Jk^a, Kell, Fy^a, Fy^b, E, Js^a, I, as well as multiple antibody specificities.

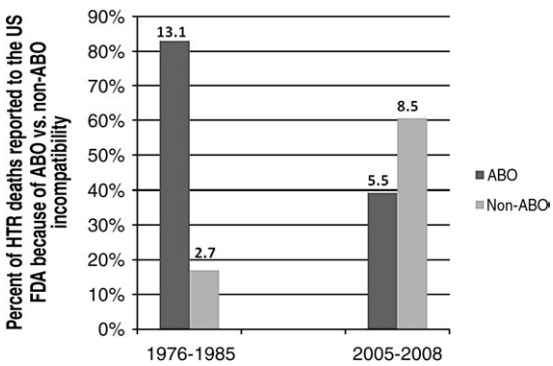

Fig 9. Proportion of deaths from acute HTR reported to the US FDA secondary to ABO vs non-ABO HTRs in 2 periods separated by 20 years. The mean annual number of deaths recorded in each period is shown above each column.

Although the possibility has been considered that the formation of RBC alloantibodies may represent a random process,[171] this does not appear to be the case.[172-178] Only 1% of the nonchronically transfused patients receiving RBCs matched for the ABO and D antigens form RBC alloantibodies,[172] but the formation of a first RBC alloantibody identifies a patient as a "high responder" to subsequent RBC alloantigen challenges. Thus, once a patient has already formed RBC alloantibodies, the probability of forming additional RBC antibodies after further RBC transfusions is 20% to 25%.[173,174]

Remarkably, this probability is the same for hemato-oncology[174] and non–hemato-oncology[173] patients, despite the fact that hemato-oncology patients receive intensive immunosuppressive treatments. In the retrospective cohort studies of Shonewille et al[173,174] that spanned periods of approximately 20 years, hemato-oncology patients received more RBC units in more ABT episodes (7 U in 3 episodes) than non–hemato-oncology patients (2 U in 1 episode) before additional RBC alloantibodies were detected. However, hemato-oncology patients experience multiple transfusion events in a short period, which probably causes overestimation of the number of transfusions needed for additional antibody formation in hemato-oncology patients, as compared with obstetrical, surgical, and other medical patients.

The current standard of care requires provision of only ABO- and D-matched RBCs for patients who have not made alloantibodies to other RBC antigens. For patients who have formed alloantibodies, transfused RBCs must be negative for all antigens to which a prospective recipient has detectable antibodies. Thus, when multiple antibodies are present (or in the process of being formed), complex serologic workups are necessary before compatible RBC units can be issued by the blood bank. No antibody detection method is capable of identifying all clinically significant RBC alloantibodies, however. Acute HTRs still occur, either because a clinically significant RBC alloantibody is missed or because fully compatible RBC units are not available when needed. In such cases, hemolysis of the transfused RBCs because of preexisting RBC alloantibodies to non-ABO antigens can cause both morbidity and mortality.

Currently, we cannot identify patients who will respond to RBC transfusions with formation of RBC alloantibodies. Patients with hemoglobinopathies are especially prone to form multiple alloantibodies,[178] which generate complex serologic workups and cause delay in the provision of compatible blood along with delayed HTRs and sometimes also acute HTRs. To prevent such problems, the standard of care has been elevated at many US hospitals for patients with hemoglobinopaties.[179] These multiply-transfused patients receive units matched for the C, E, and K (and sometimes also for the Jk^a and Fy^a) antigens, for preventing the formation of alloantibodies to these antigens.[179-182] Such extended antigen matching between donor and recipient is generally performed phenotypically, that is, using the traditional serologic techniques of hemagglutination.[173] A driving force for doing extended antigen matching for patients with hemoglobinopathies has been the difference between donor and recipient phenotypes due to ethnic-pool gene diversity.[183,184]

Extended phenotypic antigen matching is generally not performed for other multiply-transfused patients either because the clinical benefit from such an elevated standard of care has not been empirically documented or because the additional effort generated by the extended phenotypic matching is considered to be prohibitive. Genotyping for C, E, K, Jk^a, Fy^a, and other clinically significant RBC antigens is now available, however, and it can be performed on patients as well as donor units (using DNA extracted from the residual WBCs in WBC-reduced RBC units).[185-189] The feasibility of providing extended antigen matching between donor and recipient through genotyping was recently demonstrated in a multicenter US study for several categories of patients (in addition to patients with sickle cell disease).[190] This study used random-donor units from existing inventories, and it used a computerized inventory management system to create and maintain an inventory of genotyped units, as well as identify compatible blood for transfusion recipients at increasingly stringent levels of antigen matching.

Transfusion-Associated GVHD

Transfusion-associated GVHD results from the engraftment of donor lymphocytes, which proliferate and mount an immune attack against the recipient, destroying the recipient's tissues. The disease is 90% fatal. Immunocompromised patients who cannot clear the donor lymphocytes, and patients who receive blood components from

donors (eg, relatives) with whom they partially share HLA haplotypes, are at risk for GVHD and must receive irradiated components. Irradiation always prevents GVHD, yet sporadic cases do occur. In 1996 to 1999, 12 fatal cases were captured by the SHOT system (4/y),[15,16] although there has been only 1 further case after universal WBC reduction was implemented.[191] Of the 13 cases, 2 patients were not known to be immunocompromised at the time of their transfusion; 6 had B-cell malignancies not listed as an indication for irradiation in the United Kingdom, and 5 were apparently immunocompetent (although there may have been partial haplotype sharing between donor and recipient).[15]

A higher risk of TA-GVHD has been reported from Japan where the population is racially homogeneous and likely to share HLA haplotypes. Four of 847 patients receiving fresh (<7-day-old) blood for cardiac surgery developed TA-GVHD.[192] Rososhansky et al[193] estimated that 1 per 2000 patients transfused in the United States may share an HLA haplotype(s) with a donor. This figure is far higher than the reported number of TA-GVHD cases, perhaps because blood transfused in the United States is more than 7-day-old and does not contain viable lymphocytes. Some hospitals (especially cancer and pediatric centers) irradiate all blood transfused to their patients because (1) patients at risk for TA-GVHD may not receive irradiated blood due to errors, (2) there is no consensus on the list of conditions that render a patient at risk for TA-GVHD,[194] and (3) some apparently immunocompetent patients do develop TA-GVHD. The WBC-reduced components do not eliminate the risk of TA-GVHD, although it may be possible to develop WBC reduction technologies in the future capable of doing so.[195]

Other Noninfectious Complications

As recognition of TACO improved, 17 deaths were attributed to TACO by the FDA in 2005 to 2008,[1] making TACO the fourth most frequent cause of reported transfusion-related deaths (Figs 1 and 2). In patients with diminished cardiac reserve or chronic anemia, rapid transfusion can precipitate acute pulmonary edema secondary to congestive heart failure. Even small transfusion volumes may cause TACO, especially in infants and the elderly. Transfusion-associated circulatory overload has been reported to occur in 1 per 3168 transfused patients,[196] and even in 25 of 49 patients transfused in the ICU.[197]

There are various other potentially fatal reactions occurring within 24 hours of a transfusion, including anaphylaxis, TA hypotension, bleeding associated with the dilution of platelets and clotting factors, metabolic disorders, and others.[4] Anaphylaxis is triggered by proteins contained in transfused donor plasma, and it has caused fatalities in patients with IgA deficiency and preformed anti-IgA antibodies.[198] Such patients must receive components collected from IgA-deficient donors.

Posttransfusion purpura is a sudden, dramatic thrombocytopenia developing after an ABT in a patient previously sensitized (by pregnancy or transfusion of any blood component, usually transfusion of RBCs) to a high-frequency platelet-specific antigen of the donor.[199] The anamnestic immune response produces a potent antibody that (paradoxically) destroys the recipient's own (antigen-negative) platelets in addition to the donor's (antigen-positive) platelets. Historically, mortality has been about 8%,[199] although recently there has been only 1 fatality among 44 cases captured by the SHOT system over 8 years.[15]

MORTALITY ATTRIBUTED TO ABT BY POORLY UNDERSTOOD PATHOPHYSIOLOGIC MECHANISMS

Studies have not detected a relationship between perioperative RBC transfusion to higher target hematocrits and improved clinical outcomes.[200,201] A large, retrospective cohort study has suggested that RBC transfusion may result in lower 30-day mortality in elderly patients with acute myocardial infarction when subjects are admitted with a hematocrit of less than 30% and survive for less than 2 days,[202] but an observational reanalysis of patients with acute coronary syndromes enrolled in 3 drug RCTs showed that transfused patients had higher 30-day mortality than untransfused subjects.[203]

Association of Any (Non–WBC-Reduced or WBC-Reduced) ABT With Increased Mortality

The TRICC RCT[39] found that, compared with a restrictive RBC transfusion strategy, a liberal strategy may be associated with increased in-hospital mortality in normovolemic, critically ill patients (Fig 10). These investigators randomized 418 ICU patients to a restrictive strategy arm and

420 patients to a liberal strategy arm. The former patients were transfused if the hemoglobin concentration fell to 7.0 g/dL or less; the latter if it fell to 10.0 g/dL or less. Patients allocated to the restrictive strategy arm received on average 3.0 fewer RBC units than those from the liberal strategy arm (mean ± SD of 2.6 ± 4.1 vs 5.6 ± 5.3 RBCs per patient); overall, 33% vs 0% of the patients, respectively, avoided ABT altogether ($P < .01$).

The primary outcome, 30-day mortality, was 18.7% in the restrictive strategy arm, compared with 23.3% in the liberal strategy arm ($P = .11$). The adjusted multiple organ dysfunction score (MODS) differed between the arms (mean ± SD of 10.7 ± 7.5 vs 11.8 ± 7.7, respectively; $P = .03$), and so did the change in score from baseline (3.2 ± 7.0 vs 4.2 ± 7.4, respectively; $P = .04$). Mortality during the entire hospitalization was significantly lower in the restrictive strategy arm (22.2% vs 28.1%; $P \geq .05$). The absolute risk difference in in-hospital mortality between the arms was 5.8% (95% CI, −0.3% to 11.7%; $P \geq .05$).

Compared with the restrictive strategy arm, the liberal strategy arm also experienced worse outcomes in the risk of myocardial infarction and pulmonary edema (Fig 11). Three patients (0.7%) from the restrictive strategy arm, compared with 12 subjects (2.9%) from the liberal strategy arm, developed myocardial infarction ($P = .02$). Also, 22 patients (5.3%) from the restrictive strategy arm, compared with 45 subjects (10.7%) from the liberal strategy arm, developed pulmonary edema ($P < .01$). Although the greater risk of pulmonary edema in the liberal strategy arm could be explained by the fluid overload caused by the RBC transfusion, these findings contradict what would be expected if a liberal transfusion strategy resulted in improved oxygen delivery to the myocardium, with the enhanced oxygen consumption by the myocardium producing improved myocardial function.

Murphy et al[34] linked the United Kingdom population register with the clinical, ICU, and blood bank databases of 8516 patients who had undergone cardiac surgery for 8 years (1996-2003). When transfused and untransfused patients were compared after adjustment for confounding factors, ABT was found to be associated with a higher risk of both early (30-day) and late (1-year) mortality and ischemic postoperative morbidity. Similarly, in an observational study of 248 patients, Netzer et al[35] found that ABT in patients with ALI was associated with increased in-hospital mortality. Both non–WBC-reduced and WBC-reduced ABT were associated with a significant ($P < .001$) increase in mortality, although the magnitude of the increase in risk was greater when non–WBC-reduced (rather than WBC-reduced) RBCs had been used.

Several preclinical[204-206] and clinical[207-217] observations have supported the hypothesis that ABT in general, and non–WBC-reduced ABT in particular, may be associated with multiple organ failure (MOF). The mechanisms underlying the

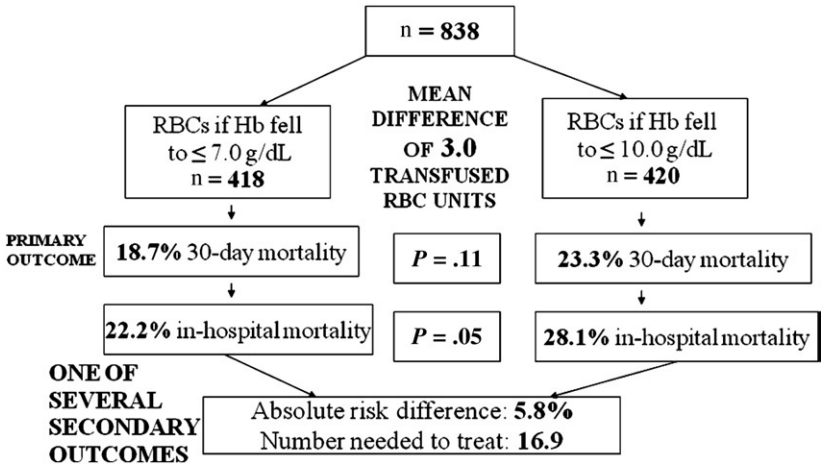

Fig 10. Design and results of the TRICC RCT.[39] There was no difference in the primary outcome (30-day mortality), but one of the mortality outcomes reported by the authors (in-hospital mortality) approached statistical significance ($P \geq .05$). If this finding is confirmed by future RCTs, it would suggest that, for every 16.9 transfused critically ill patients, 1 might die because of the 3 excess RBC transfusions received per liberal (compared with restrictive) criteria.

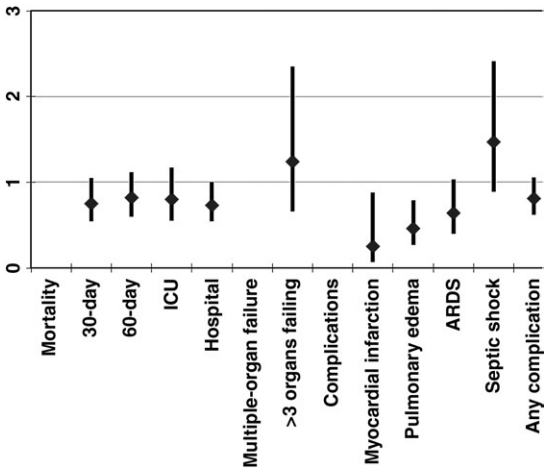

Fig 11. Clinical outcomes analyzed as categorical variables in the TRICC RCT.[39] For each comparison, the figure shows the OR of an adverse outcome in patients from the restrictive (compared with the liberal) transfusion strategy arm. Each OR is surrounded by its 95% CI. When the 95% CIs include the null value of 1, the corresponding OR is not statistically significant (ie, $P > .05$). Of 22 categorial comparisons reported by the authors, only the number of organs failing (>3 vs <3), septic shock, catheter-related sepsis, and pneumonia occurred less frequently in the liberal (compared with the restrictive) strategy arm. The differences were minimal, with only the difference in septic shock approaching a trend ($P = .13$). All other differences in categorical outcomes favored the restrictive strategy arm. Differences in any cardiac complication ($P < .01$), myocardial infarction ($P = .02$), and pulmonary edema ($P < .01$) were statistically significant, whereas the difference in ARDS ($P = .06$) approached significance. Five more outcomes were analyzed as continuous variables, and they all favored the restrictive strategy arm. Three of these differences were minimal, but the differences in adjusted MODS ($P = .03$) and for the change from baseline score ($P = .04$) were statistically significant.

development of MOF are unclear, but most evidence suggests that tissue injury is mediated by reactive oxygen species and proteolytic enzymes released from activated neutrophils.[218-220] If ABT had such a neutrophil-priming effect, the reported association between ABT and short-term mortality could reflect a "proinflammatory" effect of ABT, paralleling the bioactive-lipid/neutrophil-priming effect postulated for the pathogenesis of TRALI.[44,45]

Silliman et al[204] proposed that ABT may exercise a neutrophil-priming effect mediated by bioactive lipids that accumulate during storage. They postulated that rapidly deteriorating WBCs in stored RBCs release cytotoxic enzymes that may act on fragmented RBC membranes to produce mediators responsible for neutrophil priming and endothelial cell activation. These investigators[204,205] demonstrated that plasma obtained from stored RBCs primes neutrophils for superoxide production and enhanced cytotoxicity and also activates pulmonary endothelial cells in a dose- and age-dependent fashion. The length of RBC storage was important in these studies because no evidence of neutrophil priming was obtained when plasma stored for short periods was used. Similarly, Chin-Yee et al[206] reported that plasma supernatant from stored RBCs activates neutrophils, whereas WBC reduction of the RBC units abrogates the effect.

In the study of Johnson et al,[209] patients receiving allogeneic RBCs had a significantly higher risk of MOF than recipients of polymerized hemoglobin. Neutrophils obtained from recipients of RBCs demonstrated priming, as evidenced by increased β-2 integrin expression, superoxide production, and elastase release. Neutrophils obtained from recipients of polymerized hemoglobin showed no evidence of priming. Studies investigating the benefits obtained from placing a WBC reduction filter in the arterial line of the cardiopulmonary bypass circuit[210-212] suggested that non–WBC-reduced ABT may provoke cardiac and/or pulmonary failure. Furthermore, associations between ABT and prolonged mechanical ventilation[213,214] or MOF[208,215-217] were reported by some, but not all,[221] observational studies.

Because the RBCs transfused to the subjects enrolled in the TRICC RCT[39] were non–WBC-reduced, plausible reasons for any increase in in-hospital mortality (Figs 10 and 11), MODS, or specific complications (Fig 11) could involve pathophysiologic mechanisms relying on either WBCs[204-206,210-212] or RBCs. For the particular situation of the critically ill patients with systemic inflammatory response syndrome (SIRS) and oxidative stress enrolled in the TRICC RCT,[39] Forceville et al[222] invoked the potentially deleterious effect of the iron-containing protein (hemoglobin) that is supplied by the transfused RBCs. They reasoned that the RBCs contain iron that can amplify oxidative stress and that an increase in oxygen delivery—the purpose of an RBC transfusion—in patients with SIRS may also increase the production of toxic reactive oxygen species.[223-225] Consequently, an excess production of reactive oxygen species in subjects from the liberal transfusion arm (who received 3 more RBC units, or 600 mg of extra iron, compared with a total body iron of 2.8 g) may have worsened the preexisting oxidative stress.[225]

One unit of blood contains more than 100 times the quantity of iron absorbed daily from the diet (200 mg vs a bit >1 mg), and the iron overload and toxicity from multiple RBC transfusions are well documented.[226] A patient with a transfusion-dependent anemia requiring 2 U of RBCs per month would receive 24 U/y, or about 100 U for 4 years, thereby, accumulating 20 g of iron in her/his body. Transfused RBCs have a relatively short life span compared with the approximately 120-day life span of normal RBCs. Transfused RBCs undergo erythrophagocytosis, with release of iron that eventually overloads macrophages. When this excess iron reenters the plasma, it overwhelms the iron-carrying capacity of transferrin and is deposited in tissues as free iron. Increased iron levels become detectable 17 to 22 days after RBC transfusion. Iron overload from long-term transfusions damages the liver, heart, pancreas, thyroid, and other endocrine glands.

Forceville et al[222] therefore posited that—in a setting of SIRS, deficient antioxidant systems, and overwhelmed haptoglobin/hemopexin/transferrin systems (as could potentially have been the case in the critically ill ICU patients enrolled in the TRICC RCT[39])—the increased iron burden from the excess RBC transfusions could result in tissue injury in the acute (rather than chronic) setting. Thus, although several possibilities have been raised,[204-206,210-212,222-225] involving transfused WBCs or RBCs, the mechanism by which any (ie, either non–WBC-reduced or WBC-reduced) ABT might be associated with increased mortality—in the event that such a relationship is confirmed by future RCTs—is unknown.

Association of Non–WBC-Reduced (vs WBC-Reduced) ABT With Increased Mortality

The RCT of van de Watering et al[30]—designed to investigate an association between non–WBC-reduced ABT and postoperative infection—found, instead of that association, an association between non–WBC-reduced ABT and 60-day mortality from all causes (Fig 12).[30] The association between ABT and mortality was reported as a data-derived hypothesis,[30] and the authors postulated that non–WBC-reduced ABT may predispose to MOF, which might—in turn—predispose to mortality. These investigators undertook another RCT that confirmed the association between ABT and short-term mortality but did not find an association between non–WBC-reduced ABT and increased MOF.[31]

In the late 1990s, the United Kingdom, Canada, and several other countries implemented universal WBC reduction of cellular blood components by means of prestorage filtration, permitting "before and after" comparisons of the mortality of recipients of non–WBC-reduced RBCs before implementation of WBC reduction with the mortality of recipients of WBC-reduced RBCs after implementation of WBC reduction. Hébert et al[227] observed a

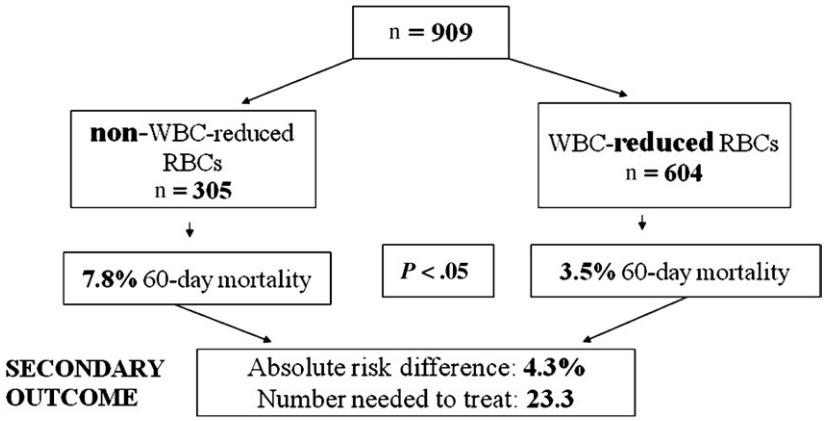

Fig 12. Design and results of the cardiac surgery RCT of van de Watering et al.[30] The authors enrolled patients into 3 arms (to receive prestorage-filtered WBC-reduced, poststorage-filtered WBC-reduced, or non–WBC-reduced RBCs), but the 2 WBC-reduced arms produced identical results and are combined here into one arm. The findings regarding the study's primary outcome (postoperative infection) were not significant, but the difference in the secondary outcome (60-day mortality) attained significance in both the 3-arm and the 2-arm comparisons. The absolute risk difference in mortality would indicate that, for every 23.3 transfused cardiac surgery patients, 1 might die because of the receipt of non–WBC-reduced (as opposed to WBC-reduced) RBCs. All platelets administered to patients enrolled in this trial had been WBC reduced.

significant (P = .04) decrease in short-term mortality (from 7.0% to 6.2%) after WBC reduction was introduced. They offered the hypothesis that the observed decrease in the number of deaths might have been due to a proinflammatory microvascular effect of transfused WBCs that affects several organ systems. This hypothesis was buttressed by the findings of a companion before and after study in premature infants.[228] In that setting, the implementation of universal WBC reduction coincided with a reduction in several secondary morbidity outcomes from several organ systems (ie, bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis)—an observation consistent with a diffuse proinflammatory microvascular effect of allogeneic WBCs (or their products). In contrast to these observations, however, a meta-analysis of all available before and after studies found neither an unadjusted nor an adjusted association of WBC reduction with decreased short-term mortality.[229]

Eleven RCTs comparing recipients of non–WBC-reduced vs WBC-reduced allogeneic RBCs have presented information on short-term (up to 3 months posttransfusion) mortality from all causes.[30-32,230-237] Across 5 RCTs conducted in cardiac surgery[30-32,234,236] that had transfused RBCs filtered before storage to the non–WBC-reduced arm, non–WBC-reduced (vs WBC-reduced) ABT was associated with a 72% increase in postoperative mortality (summary OR, 1.72; 95% CI, 1.05-2.81; $P < .05$).[238] In contrast, across 6 RCTs conducted in other settings,[230-233,235,236] non–WBC-reduced (vs WBC-reduced) ABT was not associated with any increase in postoperative mortality.[238] The adverse effect seen across these open heart surgery studies[30-32,234,236] may be associated with factors prevalent in the setting of patients undergoing cardiac surgery.

During cardiac surgery, exposure to the extracorporeal circuit, hypothermia, and reperfusion injury may generate a SIRS that is counteracted by a compensatory antiinflammatory response syndrome.[239] Any intervention by biologic response modifiers (such as, eg, the soluble mediators contained in stored non–WBC-reduced RBCs[210]) during an already existing inflammatory cascade could, thus, produce an imbalance in the SIRS-compensatory antiinflammatory response syndrome equilibrium toward SIRS. An overwhelming SIRS causes a dormant state of cell metabolism referred to as MODS, which can ultimately lead to MOF and death.[239] However, an association between non–WBC-reduced (vs WBC-reduced) ABT and MOF has not been reported by any RCT, and the mechanism by which non–WBC-reduced (vs WBC-reduced) ABT is associated with increased mortality in cardiac surgery remains unknown.[240] In the completed RCTs,[30-32,234,236] non–WBC-reduced (vs WBC-reduced) ABT was not associated with any particular cause of death, yet the aggregate mortality was higher in the non–WBC-reduced (vs the WBC-reduced) arm.[240]

SIX STRATEGIES TO FURTHER REDUCE ABT-RELATED MORTALITY

After reviewing the various causes of transfusion-related mortality in the United States today, the authors have prioritized the 6 strategies that they feel should be instituted to further reduce transfusion-related mortality. Our prioritization (summarized in Table 2) reflects our opinion that is greatly influenced by the fact that—although the risk of a new or poorly understood infectious disease with a long incubation period that can be transmitted by ABT while it is accumulating in the blood donor population before its clinical consequences become apparent remains the greatest possible threat to blood safety—to the extent that we are aware, an HIV-like emerging pathogen does not currently appear to be on the horizon. For this reason and because no pathogen reduction (PR) technology for platelets or plasma is currently licensed in the

Table 2. Six Strategies to Further Reduce ABT-Related Mortality*

1. Avoidance of unnecessary transfusions through enforcement of evidence-based transfusion guidelines
2. Prevention of TRALI by donor screening
3. Prevention of hemolytic transfusion reactions:
   (i) Augmentation of patient identification procedures by the addition of information technologies
   (ii) Prevention of additional RBC alloantibody formation in patients who are likely to need multiple transfusions in the future
4. Avoidance of pooled blood products such as pooled whole blood–derived platelets
5. White blood cell reduction of cellular blood components administered perioperatively during cardiac surgery
6. Pathogen reduction of platelet and plasma components

* Prioritized according to their impact upon reducing the number of ABT-related deaths (from highest to lowest impact strategy). This prioritization reflects the authors' opinions.

United States, we prioritized PR last among the 6 proposed strategies. In this regard, the hierarchy of strategies would change dramatically should a major transfusion-transmitted pathogen emerge, although the top strategy (avoidance of ABT through evidence-based transfusion guidelines) would likely remain at the top of our list.

Avoidance of Unnecessary Transfusions Through Enforcement of Evidence-Based Transfusion Guidelines

Transfusion of blood to bleeding patients rests on solid principles of resuscitation, tissue oxygenation, and the repletion of the vital elements of hemostasis. Many lives are saved by ABT given to bleeding patients, and in many more cases, ABT serves as an exquisite life-support measure, while other interventions are used to stop hemorrhage. In contrast, ABT given as prophylaxis because of abnormal screening test results for coagulation is associated with unfavorable risk-to-benefit ratios.[241] Each unnecessary ABT avoided through the use of transfusion guidelines is potentially tantamount to avoidance of one (or several) of the infectious and noninfectious causes of ABT-related mortality discussed here, including those deaths attributed to ABT by observational studies and RCTs through pathophysiologic mechanisms that we do not yet understand.

There is probably no other preventive strategy that can be used if ABT per se (rather than allogeneic WBCs or soluble WBC-derived mediators that accumulate in the supernatant fluid of RBCs during storage) is indeed related to all-cause mortality through such ill-defined mechanisms. If the association of any ABT (as opposed to non–WBC-reduced vs WBC-reduced ABT) with mortality were confirmed, ABT would emerge as a considerably risky medical intervention. Thus evidence-based transfusion guidelines preventing unnecessary transfusions could save more lives than a combination of all the other safety measures discussed in this review. Even if such an association is not confirmed by future RCTs, the use of evidence-based transfusion guidelines for all transfused blood components (RBCs, platelets, FFP, and cryoprecipitate) is the only strategy that can reduce the risk of—and the associated mortality from—all currently established ABT complications (Figs 1 and 2).

Transfusion of blood components has never undergone prospective randomized testing in the manner that a new drug would be expected to undergo.[242] Although the "10/30 rule" (of transfusing patients for a hemoglobin level falling to 10 g/dL or less or for a hematocrit falling to 30% or less) had been a quasi-religious belief for 5 decades,[243] the 1999 TRICC RCT[39] documented the fallacy of the previous "faith-based" indoctrination.

The delivery of oxygen and its use by tissues is only partly understood. In theory, RBCs are transfused to improve tissue oxygen delivery, although it is not always clear that such potentially increased oxygen delivery translates into increased local availability of oxygen at the tissue level, or increased intracellular consumption of oxygen,[244] nor that all microcirculatory beds respond equally to ABT.[245] Basic clinical questions that still warrant study[243,246] include the following: How do we decide which patients need RBC transfusion? Which variables should we assess to identify patients who might benefit from ABT? What are the outcomes of patients who receive one, some, or many RBC transfusions? How do we determine if a RBC transfusion is effective? Is a low hemoglobin level detrimental to the critically ill patient? If a higher hemoglobin level could be achieved without risk, would it benefit the critically ill patient?

Thus, there is now considerable interest in formulating evidence-based transfusion guidelines for nonbleeding patients. At the recent (September 2009) State-of-the-Science Symposium on Transfusion Medicine and Hemostasis held at the National Heart, Lung, and Blood Institute of the National Institutes of Health (Bethesda, MD),[247] of the 24 presented concept proposals for RCTs in transfusion medicine, 11 pertained to the formulation of appropriate indications for the transfusion of the various blood components. Of these, 5 were aimed at the development of criteria for the appropriate transfusions of RBCs, 2 at the development of criteria for the appropriate transfusions of platelets, and 5 at the development of criteria for the appropriate transfusions of FFP. Importantly, 8 concept proposals proposed to investigate the safety of lower transfusion triggers or the safety of withholding prophylactic transfusions of platelets and FFP, whereas only 3 presentations proposed to investigate possible benefits obtained from higher transfusion triggers

or from the liberal administration of prophylactic platelet or FFP transfusions.

Evidence for the appropriate indications for transfusion of RBCs in clinically stable adult or neonatal patients has been produced by RCTs conducted in North America. Such evidence is also available for the prophylactic platelet transfusions given to hemato-oncology patients with hypoproliferative thrombocytopenia, but it has not hitherto become available for prophylactic platelet or FFP transfusions administered in other settings.

Red blood cell transfusion trigger for stable adult patients. In the TRICC RCT,[39] although the difference did not attain significance in the comparison of the primary (30-day mortality) outcome ($P = .11$), allocation to a liberal (rather than restrictive) transfusion strategy arm—which resulted on average in the transfusion of 3.0 more RBC units in the ICU—was marginally associated with an increase in the absolute risk of death in the hospital by 5.8% ($P \geq .05$). This finding has not been confirmed by another RCT, and in the interim, it can be attributed to the effect of multiple comparisons, that is, the reporting of several mortality and morbidity outcomes by the authors of the TRICC RCT (Fig 11). If it is confirmed by future RCTs, it would suggest that, for every 16.9 patients receiving ABT per liberal criteria (for a hemoglobin level falling to 10 g/dL or less, as opposed to falling to 7 g/dL or less), 1 patient might die during her/his hospitalization because of the excess RBC transfusions received (Fig 10). Although such a figure is far from having been established, it would represent a staggering number of deaths secondary to ABT even if it were off by 2 orders of magnitude.

Further, RCTs are clearly needed to produce an unambiguously significant ($P < .05$) result with respect to a difference in a primary mortality outcome, as well as to determine whether the findings of the TRICC RCT[39] pertain to clinical settings outside the ICU. However, based on the existing findings,[39] physicians should endeavor to limit their patients' exposure to ABT by administering RBC transfusions to raise the hemoglobin level only when a patient's hemoglobin level falls to 7 g/dL or less (provided that the patient is not actively bleeding and does not have ischemic heart disease). Once a hemoglobin level of more than 7 g/dL (with a maintenance hemoglobin level of 7-9 g/dL in the TRICC RCT[39]) has been reached through ABT, further RBC transfusion(s) should be withheld unless a patient has symptoms or signs relating to the anemia.

This is because the TRICC RCT[39] unambiguously demonstrated that transfusion for a hemoglobin target level of less than 7 g/dL is as good as transfusion for a hemoglobin target level of less than 10 g/dL (with a maintenance hemoglobin level of 10-12 g/dL) in the absence of symptoms or signs of anemia (Fig 11). In the analysis of all patients, there were no statistically significant ($P < .05$) differences between the arms other than for the adjusted MODS (and difference from the baseline score), as well as the development of myocardial infarction and pulmonary edema. All 4 significant differences favored the restrictive strategy arm. Moreover, with the sole exception of septic shock (Fig 11), all observed trends favored the restrictive strategy arm as well. Compared with the liberal strategy arm, the patients in the restrictive strategy arm consistently demonstrated better clinical outcomes in mortality, MOF, length of stay in the hospital or the ICU, organ-specific complications, or any studied complication.[39]

Admittedly, the TRICC RCT[39] left open the possibility that both trial arms might have had a worse outcome than would have been the case had a third, "standard-of-care" arm also been included, that is, an arm in which physicians would have been allowed to use their own judgment to transfuse for a hemoglobin target level of between less than 7 g/dL and less than 10 g/dL based on their assessment of each patient's clinical presentation.[248,249] This possibility remains to be examined in future RCTs, including the recently completed Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) transfusion trigger trial.[250]

The pilot study for the FOCUS RCT showed no difference in mortality between the liberal and restrictive transfusion strategy arms.[251] Except for the TRICC RCT[39] and the pilot for the FOCUS trial,[251] there are no RCTs evaluating RBC transfusion triggers in adult patients. Therefore, at the time of this writing and for clinically stable adult patients, there is no evidence from RCTs that a "liberal" transfusion strategy (administration of blood transfusion for a hemoglobin level falling lower than any target value >7 g/dL) confers any benefit to patients compared with a "restrictive" transfusion strategy (administration of RBC

transfusion for a hemoglobin level reaching 7 g/dL or falling lower than that target).

In contrast to the overall results of the TRICC RCT[39] (which showed a trend toward reduced mortality in patients randomized to the restrictive strategy arm), the subgroup analysis of 257 patients with ischemic heart disease showed a trend toward reduced mortality in the liberal strategy arm.[252] For this reason, the FOCUS RCT[250] enrolled 2600 patients to determine whether subjects with cardiovascular disease or cardiovascular risk factors undergoing surgical repair of hip fracture benefit from a higher (<10 g/dL) vs lower (<8 g/dL) transfusion trigger. When the findings of FOCUS are finally presented, it is to be hoped that they will end the debate whether the recommendation[253] to use RBC transfusion to maintain hemoglobin levels greater than 10 g/dL in high-risk patients should be adhered to. The rationale[253] for transfusing patients with impaired ventricular function to a hemoglobin level more than 10 g/dL has been that the lack of compensatory increase in cardiac output leaves ABT as the only means to increase oxygen delivery postoperatively.

Red blood cell transfusion trigger for stable low birth weight neonates. The benefit from a liberal vs restrictive transfusion strategy (vs the clinical equivalence of the 2) also remains to be elucidated in low birth weight preterm infants. The Canadian Premature Infants in Need of Transfusion RCT that enrolled 451 neonates with a birth weight of less than 1 kg recorded a composite outcome of 74.0% in the restrictive strategy arm vs 69.7% in the liberal strategy arm ($P = .25$). The composite outcome consisted of death before discharge from the hospital, survival with severe retinopathy, bronchopulmonary dysplasia, and/or brain injury on cranial ultrasound.[254]

Owing to multiple exclusion criteria, the neonates enrolled in the Premature Infants in Need of Transfusion trial[254] may have had a "better-than-average" prognosis. Recently, these same infants had their neurodevelopmental outcomes assessed at 18 to 21 months of age.[255] There was no statistical difference in the primary outcome (death or presence of cerebral palsy, cognitive delay, or severe visual or hearing impairment), which was found in 45% of the infants from the restrictive arm and 38% of the infants from the liberal arm. There was also no difference in any of the preplanned secondary outcomes. However, the difference in cognitive delay (Mental Development Index score of <70) approached statistical significance. A post hoc analysis, with the Mental Development Index score redefined as <85, showed a statistically significant difference favoring the liberal strategy arm.[255] A small US RCT enrolling 100 infants with a birth weight of between 0.5 and 1.3 kg concluded that infants in the restrictive strategy arm were more likely to have intraparenchymal brain hemorrhage or periventricular leukomalacia, and they also had more frequent episodes of both mild and severe apnea.[256] These conclusions, however, were based on a very small number of events (with 0 vs 4 and 0 vs 6 infants, respectively, having grade IV brain hemorrhage or grade IV brain hemorrhage and/or periventricular leukomalacia) and any benefit from a liberal transfusion strategy needs to be investigated further in future RCTs.

Prophylactic platelet dose for hemato-oncology patients. The Prophylactic Platelet Dose on Transfusion Outcomes (PLADO) RCT[257] concluded that it is safe to transfuse platelets prophylactically to hemato-oncology patients with hypoproliferative thrombocytopenia—when the 10 000 platelets/μL trigger is reached—at a dose half the customary dose. Data were analyzed on 1272 patients hospitalized at 26 trial sites who received at least 1 platelet transfusion. Patients were transfused prophylactically for monitoring platelet counts of less than 10 000/μL or at a different transfusion trigger (or dose) if therapeutically indicated.

Whether the end point was bleeding of World Health Organization (WHO) grade 2 or greater or bleeding greater than grade 2, the same proportion of patients developed bleeding, whether they were assigned to receive half the standard dose, the standard dose, or twice the standard dose, that is, respectively, 1.1×10^{11} platelets/m^2, 2.2×10^{11} platelets/m^2, or 4.4×10^{11} platelets/m^2, corresponding to half of a single-donor concentrate, one single-donor concentrate, or 2 single-donor concentrates or an equivalent dose of pooled whole blood–derived platelets. The most common bleeding sites were the gastrointestinal tract and the genitourinary tract. The was no difference in bleeding sites among the 3 arms, with the exception of oral bleeding that was more common in the half-the-standard-dose arm compared with the standard-dose and twice-the-standard-dose arms. Regardless of randomization

arm, subjects with a monitoring platelet count of less than 5000/μL had the highest bleeding risk. Equivalent bleeding risk was observed for platelet counts between 6000/μL and 80 000/μL. There was also no difference between the arms in the number of RBC units transfused.

The WHO grade 2 bleeding included gross bleeding such as hematuria, hematemesis, and others; grade 3 bleeding required RBC transfusion; and grade 4 bleeding was life- or organ-threatening. The median number of days with greater than grade 2 bleeding was 1 in all 3 arms. Patients were stratified by cause of hypoproliferative thrombocytopenia (chemotherapy for hematologic malignancy or for solid tumor vs autologous or allogeneic bone marrow transplant), and platelet dose did not affect bleeding in any patient stratum. Patients receiving half the standard dose had more transfusion episodes than patients from the other 2 arms (5, 3, and 3 episodes, respectively; $P < .001$), but they were also transfused a lower total number of platelets (median of 11×10^{11}, 12×10^{11}, and 22×10^{11}, respectively). Although the difference in the total transfused dose of platelets received by the half-the-standard-dose vs the standard-dose arm was small (9%), it was statistically significant ($P = .02$).

Based on the findings of the PLADO RCT,[257] RCTs are now being designed to investigate whether it might be safe to altogether abandon the practice of prophylactic platelet transfusions to hemato-oncology patients for less than 10 000 platelets/μL and to instead transfuse platelets only therapeutically (when patients have clinical bleeding sufficient to require intervention).[258] Nonetheless, the Strategies for the Transfusion of Platelets RCT[259]—which similarly compared low-dose and standard-dose prophylactic platelet transfusions—was terminated early by the Data Safety Monitoring Board because a 5% difference (a prespecified stopping rule for that trial) in WHO grade 4 bleeding was reached. At that time, 3 (5.2%) of 58 patients in the low-dose arm, vs 0 (0%) of 61 patients in the standard-dose arm, had had grade 4 bleeding. The same proportion of patients (30/58 in the low-dose arm vs 30/61 in the standard-dose arm) had experienced grade 2 or greater bleeding. However, there was no difference in the number of donor exposures between the 2 arms (mean ± SD of 26.3 ± 28.2 in the low-dose vs 22.2 ± 15.6 in the standard-dose arm, $P = .34$), with the mean (±SD) interval between transfusions (in days) being, respectively, 1.8 ± 1.1 vs 2.8 ± 1.8.

Neither the PLADO[257] nor the Strategies for the Transfusion of Platelets[259] RCTs had used exclusively single-donor (apheresis) platelets. If the low-dose arm in this clinical setting needs platelet transfusions every 1.8 ± 1.1 days,[259] however, it should be possible to devise an inventory management practice whereby the second half of a single-donor platelet concentrate is administered to the same patient when the subject is an in-patient and requires a second platelet transfusion within the shelf life of the product. (According to many clinicians, outpatients might be better off receiving the standard dose to maximize the interval between platelet transfusions.) In this manner, by relying exclusively on split apheresis platelet concentrates, the 9% reduction in the total number of transfused platelets ($P = .02$) demonstrated by the PLADO RCT[257] could translate into a clinically significant reduction in the number of donor exposures for hemato-oncology patients supported with prophylactic platelet transfusions at half the dose that is currently regarded as "standard."

Other prophylactic platelet and FFP transfusions. An extensive body of evidence from observational studies indicates that patients with moderately decreased platelet counts (>20 000/μL) or moderately elevated international normalized ratios (INRs) (<3) who underwent a variety of invasive procedures (central venous catheter insertion, liver biopsy, thoracocentesis or paracentesis, gastrointestinal endoscopy and biopsy, tracheotomy, bronchoscopy and transbronchial biopsy, renal biopsy, diagnostic lumbar puncture, epidural anesthesia, neurologic procedures, or angiography) without receiving a transfusion of platelets or FFP did not bleed more often than did patients who received prophylactic platelet or FFP transfusion before the procedure.[241] In the absence of coagulopathy, the available observational studies suggest that a platelet count of greater than 20 000/μL is adequate for performing these procedures without a prophylactic platelet transfusion. Conversely, with a platelet count of greater than 50 000/μL, the available observational studies suggest that an INR of less than 3 is adequate for performing these procedures without the need for a prophylactic plasma transfusion.[241]

There are no data from RCTs, however, to support the safety of such conservative transfusion

triggers, and thus, liberal transfusion guidelines for prophylactic platelet and FFP transfusions are used at many US institutions, in accordance with available (published) transfusion guidelines.[260-268] The safety of these triggers (platelets of <20 000/μL in the absence of coagulopathy and INR of >3 when the platelet count is >50 000/μL) is unlikely to be demonstrated by RCTs in the foreseeable future because an RCT using clinical bleeding as the primary end point would have to enroll a prohibitively large number of patients to establish any difference between the arms. This is because a very small proportion of subjects from either the conservative or the liberal strategy transfusion arm are expected to bleed.

The College of American Pathologists' 1994 guidelines[261] recommend transfusion of FFP when the coagulation times are greater than 1.5 times the midpoint of the normal range in the laboratory performing the tests. The Canadian Medical Association 1997 guidelines[262] state that "plasma may be administered to prepare for surgery or liver biopsy when the results of coagulation assays are deemed sufficiently abnormal. Prophylactic plasma transfusion is not indicated for certain invasive procedures (eg, percutaneous liver biopsy, paracentesis, thoracentesis) in patients with liver disease if their INR is 2.0 or less."

After a review of data from observational studies in which procedures were performed on patients with platelet counts less than 100 000/μL, less than 50 000/μL, or even less than 20 000/μL without prophylactic platelet transfusions, the American Society of Clinical Oncologists' 2001 panel[264] concluded that a platelet count of 40 000 to 50 000/μL suffices for performing lumbar puncture, liver biopsy, gastrointestinal endoscopy, fiberoptic bronchoscopy and bronchoalveolar lavage, transbronchial biopsy, central venous catheter insertion, and tooth extraction. The panel further observed that "there are sparse data about the safety of invasive procedures at much lower count levels." However, with the exception of bone marrow aspiration and biopsy (which can clearly be performed safely at counts of <20 000/μL), the panel stopped short of making a recommendation because it was "difficult to draw firm data-driven conclusions as to the lower level of platelet count that is safe for these various procedures." The panel accordingly concluded that "more systematic research in this area is clearly needed."

The British Committee for Standards in Hematology guidelines for the use of platelets and FFP in massive transfusion anticipate coagulation times of greater than 1.5 times the mean normal values after replacement of 1 to 1.5 times the patient's blood volume and a platelet count of less than 50 000/μL after replacement of 2 times the patient's blood volume.[265,266] According to the 2003 British Committee for Standards in Hematology guidelines, transfusion of FFP and platelets is indicated when these triggers are reached. The 2006 guidelines, however, recommend that a "margin of safety" be allowed to ensure that the platelet count remain at less than 50 000/μL. Toward this end, a platelet transfusion trigger of less than 75 000/μL is recommended for a patient with on-going bleeding, with the trigger increased to less than 100 000/μL for a patient with multiple or central nervous system trauma.[267]

Even in a prophylactic setting, a platelet transfusion trigger of less than 50 000/μL is recommended before lumbar puncture, epidural anesthesia, gastroscopy and biopsy, insertion of indwelling lines, transbronchial biopsy, liver biopsy, and laparatomy or similar procedures. For operations in critical sites—such as the brain or the eyes—the platelet transfusion trigger is set at less than 100 000/μL. Nonetheless, bone marrow aspiration and biopsy can be performed even in patients with severe thrombocytopenia without platelet transfusion support.[267] The US transfusion guidelines for plasma, based on a systematic review of all the available clinical studies, are expected from the AABB in the near future.

Prevention of TRALI by Donor Screening

Our current single-donor and pooled whole blood–derived platelets—which are collected without regard to donor sex or the presence of WBC antibodies in the donor—are probably associated with an approximately equal risk of TRALI.[102] Although a whole blood–derived concentrate contains 4 to 6 times less plasma from any individual donor (who may be a female multiparous donor with WBC antibodies matching the recipient's antigens), a recipient of a platelet pool has a 4 to 6 times greater risk of receiving a 50-mL concentrate from a female multiparous donor with WBC antibodies matching the recipient's antigens, and 50 mL of donor plasma are sufficient to cause TRALI.[133] When all transfused patients are

considered, the higher probability of exposure to 50 mL of plasma from such a donor probably carries as much risk on average as the receipt of 4 to 6 times as much plasma from an individual donor of single-donor platelets (who may similarly have antibodies matching the recipient's antigens).

Also, the available limited data[41,43,127] comparing the risk of TRALI from pooled whole blood–derived vs single-donor platelets (Table 3) do not indicate any difference in risk between the 2 types of components.[102] Importantly, no empirical evidence has been adduced[108] to support the opposite opinion that, compared with pooled whole blood–derived platelets, single-donor platelets carry a greater risk of TRALI. The latter view continues to represent a theoretical prediction made in 1994 based on the antibody hypothesis of TRALI pathogenesis[5]—a prediction that has been continuously carried forward based on case reports and small case series but no controlled studies.

Data from observational[43] (as opposed to passive surveillance) studies—directly comparing all consecutive recipients of single-donor vs pooled whole blood–derived platelets in the same setting—are needed to calculate any relative risk of TRALI from single-donor vs pooled whole-blood-derived platelets. In the absence of such reports, active surveillance studies[2,42] conducted at sentinel sites that transfuse both single-donor and pooled whole-blood-derived platelets can be informative. Until such data are reported, however, it is impossible to reach any definitive conclusion about the relative risk of TRALI in association with single-donor vs pooled whole blood–derived platelets from the available conflicting databases.[102]

If our current single-donor and pooled whole blood–derived platelets are associated with an approximately equal risk of TRALI (Table 3)[102,108] and single-donor platelets in the future are collected solely from male donors or female donors without a history of pregnancy or shown not to have WBC antibodies, these future single-donor platelets should be associated with a lower risk of TRALI than our current pooled whole blood–derived platelets. A mathematical model[108] considered that

Table 3. Systematic Review of Studies Diagnosing TRALI Based on the Canadian Consensus Criteria[11] in Settings Transfusing Both Single-Donor and Pooled Whole Blood–Derived Platelets[102]

Study (study design)	Risk of TRALI in association with pooled whole blood–derived vs single-donor platelets
Robillard et al[41] (passive surveillance, Public Health Agency of Canada; cases of TRALI)	1 per 8847 (2004) or 1 per 40 452 (2005) pools of 5 whole blood–derived concentrates vs 1 per 11 354 (2004) or 1 per 46 996 (2005) single-donor platelet concentrates
Gajic et al[43] (nested case-control study of 74 TRALI cases and 74 controls, conducted as part of a prospective observational study of 901 patients sequentially admitted to a medical ICU)	The cases received 10 single-donor concentrates and 6 platelet pools The controls received 3 single-donor concentrates and 3 platelet pools Although the cases received more platelet transfusions than the controls ($P = .06$), the type of transfused platelet component did not differ from what would be expected by the composition of the local blood bank inventory at the time of the study*
Eder et al[127] (passive surveillance, American Red Cross; deaths from TRALI)	1 per 2 157 883 distributed individual whole blood–derived platelet concentrates; or 1 per 359 647 pools of 6[56] whole blood–derived platelet concentrates; or 1 per 279 805 transfused pools of whole blood–derived platelets† vs 1 per 320 752 distributed single-donor platelets; or 1 per 285 630 transfused single-donor platelets†

* Approximately 50% single-donor and 50% pooled whole blood–derived platelets.

† Given that 22.2% of distributed individual whole blood–derived platelet concentrates outdate, as compared with 10.9% of distributed single-donor platelet concentrates.[56]

the TRALI risk associated with future single-donor platelets (collected from male donors or appropriately screened female donors) would be 40% to 80% lower than the risk of TRALI associated with our current single-donor or pooled whole blood–derived platelets.

Because TRALI is the leading cause of transfusion-related mortality in the United States today (Figs 1 and 2), moving to an all-apheresis platelet supply that would rely exclusively on male donors or female donors without a history of pregnancy or shown not to have WBC antibodies would be a major improvement in transfusion safety, replicating to some extent the success story presumably realized by the conversion to male-only FFP (Figs 5 and 6). It was recently estimated that the exclusion of female donors who have circulating WBC antibodies would result in a loss of only 6% of our current US plateletpheresis donors.[147] It should thus be possible, through donor recruitment efforts, to both replace this small percentage of our current plateletpheresis donors and attract additional plateletpheresis donors to harvest the 12.5% of therapeutic platelet doses that continue to be provided as pooled whole blood–derived platelets in the United States.

In addition to reducing the risk of TRALI, an all-apheresis platelet supply will effect a significant reduction in the risk of TTIs and TAS (Table 4), which cannot yet be effected in the United States through PR of platelets. Because of the combined effect of an all-apheresis platelet supply on 2 of the 3 leading causes of transfusion-related mortality in the United States today (TRALI and TAS), as well as the reduction in the risk of an HIV-like or WNV-like agent to emerge in the future, we believe that an all-apheresis platelet supply that relies exclusively on male donors, female donors without a history of pregnancy, and female donors shown not to have WBC antibodies may be second only to conservative transfusion guidelines in the impact that it can have upon reducing transfusion-related mortality in the United States today.

Although our recommendation for an all-apheresis platelet supply is based solely on safety, a concurrent possible benefit that has not hitherto been as well documented in the literature may be the increased efficacy of single-donor (compared with pooled whole blood–derived) platelets in treating patients with thrombocytopenia. A study of radiolabeled autologous platelets, done in volunteers, showed that platelet recovery and survival were significantly better with single-donor (compared with whole blood–derived) platelets.[269] Also, a meta-analysis of 5 RCTs showed that the 1-hour and 24-hour corrected count increments were significantly higher after single-donor (compared with pooled whole blood–derived) platelet transfusion.[270] In patients with leukemia receiving prophylactic platelet transfusions in the first 100 days after stem-cell transplantation, single-donor (compared with pooled whole blood–derived) platelets produced better corrected count increments, although both components were equally effective in preventing hemorrhage in this small study.[271]

Prevention of Hemolytic Transfusion Reactions

Augmentation of patient identification procedures. The continued occurrence of fatalities from ABO HTRs (Fig 9)—an ABT hazard whose root cause is virtually always human error and a logistical problem that we have been trying to solve since the 1970s—are both deplorable and inexcusable. It is hard to understand why the implementation of information technologies that would supplement (rather than replace) the proper patient identification procedures at the time of collection of the pretransfusion sample and—even more important—at the time of transfusion of the donor unit to the recipient has not yet been mandated by US regulatory agencies (such as the FDA or the Joint Commission for Accreditation of Hospitals).

Four decades of fatalities secondary to ABO HTRs have demonstrated that relying solely on medical professionals to prevent this hazard by always following proper procedure is inadequate. In-depth training of the transfusionists and strict adherence to proper procedure should now be supplemented by robust information technologies.

Prevention of additional RBC alloantibody formation. Fatalities from non-ABO HTRs (Fig 9) may require a more far-reaching change in our blood banking practices for their prevention, and the appropriateness of this change continues to be debated.[175] The data of Shonewille et al[173,174] would argue for the introduction of extended antigen matching for preventing the formation of additional RBC alloantibodies in all patients who have already formed their first RBC alloantibody. The probability of forming additional RBC antibodies with further RBC transfusions is 20% to

Table 4. Expected Annual Reduction in the Number of TTI Cases Contracted in the United States Through Platelet Transfusion if All Therapeutic Platelet Doses Were Provided as Single-Donor Platelets

10.388 million whole blood–derived equivalent platelet units transfused in the United States in 2006*
—9.092 million (87.5%) provided as single-donor platelets
—1.296 million (12.5%) provided as pooled whole blood–derived platelets
For therapeutic platelet doses provided as pooled whole blood–derived platelets
—1.296 million whole blood donors were used
—These patient needs could have been met instead by 216 000 donors of single-donor platelets
—Thereby avoiding 1.080 million exposures of transfusion recipients to allogeneic donors

Risk of TTI in the United States today†	Expected annual reduction in the number of cases of TTIs if 1.080 million allogeneic donor exposures are prevented	
	Best case scenario‡	Worst case scenario‡
HIV: 1 per 2.135 million donations[63]	0.17	0.50
HCV: 1 per 1.935 million donations[63]	0.19	0.56
HBV: 1 per 0.280 million donations[63,67,68]	1.29	3.87
TAS: 1 per 12 000 platelet pools§	15.0	15.0
Next WNV-like pathogen to emerge¶	9.9	29.7
Next HIV-like pathogen to emerge	36.1	108.2

NOTE. Assuming that, at the peak of the epidemic before measures are introduced to interrupt transmission through ABT, the next HIV-like pathogen to emerge in the future will have reached a prevalence of 1 per 10 000 donations in the population of eligible US blood donors.[102]

* According to Whitaker et al.[56] The median number of whole blood–derived platelet concentrates per platelet pool was observed to be 6 for US hospitals.

† Based on published mathematical models of the residual risk of transmission of HIV, HCV, and HBV because of "window period" infections.[64-68]

‡ A best case scenario indicates a smaller relative risk of transmission of pathogens by transfusion of pooled whole blood–derived (vs single-donor) platelets because (1) one single-donor concentrate can be equivalent to as few as 4 whole blood–derived platelet concentrates; (2) a significant proportion (64%[56] or greater) of single-donor concentrates represent split products, so that an infected plateletpheresis donor can infect 2 (or occasionally even 3) rather than 1 recipient; and (3) an infected plateletpheresis donor can donate more than once during the "window period" of at least some TTIs (eg, HBV infection). A worst case scenario indicates a greater relative risk of transmission of pathogens by transfusion of pooled whole blood–derived (vs single-donor) platelets because (1) one single-donor concentrate was observed to be equivalent to a pool of 6 whole blood–derived concentrates in actual US practice by Whitaker et al[56] (range of <5 to >10; median of 6); (2) a higher proportion of plateletpheresis (compared with whole-blood) donors are repeat donors, thereby, presumably having a lower risk of incident HIV, HCV, or HBV infection; (3) patients receiving a pool of 4 whole blood–derived platelet concentrates may receive transfusion of a second pool as well (if they have an inadequate corrected count increment); and (4) dose escalation is the usual approach to nonimmune causes of platelet refractoriness and recipients of either pooled whole blood–derived or single-donor platelets may receive a second (or even third) therapeutic platelet dose as well. In the latter case, pooled whole blood–derived platelets would expose a recipient to considerably more donors than single-donor concentrates. Thus, these best and worst case scenarios were deemed to represent the 2 extremes of the plausible range of the annual number of cases of TTIs that could be prevented if all therapeutic platelet doses in the United States were provided as single-donor concentrates.[102]

§ Assuming that all pooled whole blood–derived platelets distributed in the United States will soon be prepooled and cultured (Fig 7).

¶ Reproducing the WNV experience from the summer and fall of 2002. For these calculations, it is assumed that 380 infections[75] would be contracted through ABT and that all blood components made from whole blood are equally infectious.[102]

25% in such patients.[173,174] The formation of such additional alloantibodies can be associated with complex serologic workups, delay in the provision of compatible blood, as well as delayed and acute HTRs. Preventing the formation of additional RBC alloantibodies would be a significant move toward optimal transfusion safety.

According to Shonewille et al,[173] if extended antigen matching between donor and recipient were restricted to the antigens with the highest immunization risk (ie, C, c, E, K, Fy^a, and Jk^a), finding compatible blood donors would be routinely feasible in the Netherlands. Finding compatible donors would be problematic, however, if the extended matching of donor and recipient were to also include the Jk^b and S antigens. Although it can be debated how extensive the extended antigen matching between donor and recipient ought to be and whether it should be offered to all transfusion recipients who have made their first RBC alloantibody or reserved for selected categories of alloimmunized patients, we believe that the time has come for the principle of extended antigen matching between donor and recipient to be

widely endorsed and implemented. At a minimum, extended antigen matching should include the C, E, and K antigens, as well as extend to hemato-oncology patients in addition to patients with hemoglobinopathies.

Because the prevalence of RBC alloantibodies in hemato-oncology patients ranges between 9% and 13%[272,273] and these patients have a 20% to 25% chance of forming additional RBC alloantibodies once they have formed their first antibody, we believe that already alloimmunized hemato-oncology patients should be offered the same standard of care as patients with sickle cell disease in whom the prevalence of alloimmunization ranges between 19% and 43%.[274] When a blood bank uses genotyping (rather than phenotyping) of donors and recipients, as well as an electronic inventory management system for doing the extended antigen matching between the two, it should be possible to expand extended matching beyond the C, E, and K antigens and beyond the hemato-oncology patients and patients with hemoglobinopathies, without an insurmountable rise in our workload.[190]

Clearly, avoiding RBC alloimmunization will be of benefit to any patient, and the technology is rapidly advancing to support an extended donor genotype repository and routine extended antigen matching between donor and recipient. The counterargument relates to the magnitude of the expected benefit and consequently to the cost-benefit ratio associated with genotype technology vs other technologies discussed in this review (as well as others) and other necessary functions presently vying for our resources.[175] For patients with sickle cell disease, the higher standard of care can be justified because the inflammatory response associated with the transfusion reaction can provoke sickle cell crisis, stroke, or other severe complications. This considerable benefit does not apply to the alloimmunized hemato-oncology patients (or other alloimmunized transfusion recipients) for whom extended antigen matching is intended to prevent the morbidity and mortality associated with acute and delayed HTRs. Yet, although deaths from delayed HTRs are exceedingly rare,[275] the passively reported deaths from non-ABO HTRs shown in Figure 9 make extended antigen matching between donor and recipient a safety measure very worthy of implementation.

Avoidance of Pooled Blood Products Such as Pooled Whole Blood–Derived Platelets

In the absence of PR and based on past experience with HIV and HCV,[22,23] an HIV-like pathogen that could emerge in the future remains the greatest threat to blood safety. Moreover, even the PR methods under development could not protect the blood supply from all the emerging agents prioritized by the AABB Task Force.[29] For example, of the agents listed in that report,[29] pathologic prions, human parvovirus B19, and hepatitis A virus would not be inactivated or would probably be inadequately inactivated by PR. It should also be borne in mind that the very concept of emerging infections is that their evolution and manifestations, as well as the properties of the associated pathogen, are intrinsically unpredictable. This is because PR procedures are almost always validated against transfusion-transmitted agents that are already known.[276] Thus, emerging infections may be neither inactivated by PR nor associated with specific high-risk groups whose deferral from blood donation could prevent transmission to transfusion recipients. The latter would be the case if the next major transfusion-transmitted pathogen to emerge were foodborne (such as vCJD), vector-borne (such as WNV), or even airborne (such as Severe Acute Respiratory Syndrome).[102,277]

Therefore, reducing the number of donors to whom a patient is exposed is the only strategy that can reduce the risk of transmission of any TTI that might emerge in the future.[26,102] Most of the success of this strategy depends on the prevention of unnecessary transfusions through the enforcement of evidence-based transfusion guidelines on the hospital side, but a lot can be accomplished on the blood center side as well, by avoiding the distribution of pooled blood products, especially pooled whole blood–derived platelets.[26,102]

To provide the same therapeutic benefit to a recipient that could be obtained from the transfusion of a single-donor platelet concentrate, pooled whole blood–derived platelets expose a patient to 4 to 6 times as many donors as an apheresis product. Table 4 shows the number of cases of TTIs that could be prevented annually in the United States if the United States provided all therapeutic platelet doses transfused to patients in the form of single-donor concentrates.

Despite these figures, there is debate in the United States as to whether it is appropriate to

revert to providing prepooled and cultured whole blood–derived platelets, as an alternative to providing single-donor platelets collected exclusively from male donors, female donors without a history of pregnancy, or female donors shown not to have WBC antibodies, based on the 2006 AABB recommendations for TRALI prevention.[8,102] Historically,[2,5] single-donor platelets have been considered by many to be associated with a higher risk of TRALI compared with pooled whole blood–derived platelets because they contain 4 to 6 times as much plasma from a single donor, which can potentially be collected from a female donor who has previously been pregnant and has circulating WBC antibodies directed against the recipient's antigens.

Yet, albeit few,[128-132] there have been reports of TRALI associated with pooled whole blood–derived platelets, and TRALI has been documented to occur in association with the transfusion of blood components containing as little as 10 mL of plasma.[133] A higher risk of TRALI in association with single-donor (compared with pooled whole blood–derived) platelets has not been documented by an observational study or RCT comparing the 2 types of platelet components in a setting where both types of platelet concentrates are transfused to the same patient population under the same conditions and at the same time.

A recent systematic review of the literature[102] retrieved only 3 studies[41,43,127] that had diagnosed TRALI based on the Canadian consensus criteria[11]—in "real time" and in settings transfusing both single-donor and pooled whole blood–derived platelets—and had reported the risk of TRALI separately for single-donor platelets vs either whole blood–derived platelets or platelet pools. Table 3 summarizes the attributes and findings of the 3 studies[41,43,127] included in the systematic review.[102] All 3 studies[41,43,127] observed that the risk of TRALI was approximately equal per single-donor concentrate or per pool of whole blood–derived platelets.

The absence of any recent TRALI deaths attributed to pooled whole blood–derived platelets and reported passively to the FDA[1] (Fig 13) has featured in the debate over whether the United States should increase its reliance on prepooled and cultured whole blood–derived (vs single-donor) platelets. Some observers have reasoned that because 12.5% of therapeutic platelet doses continue to be provided as pooled whole blood–derived platelets in the United States,[56] 1 to 2 TRALI fatalities ascribed to pooled whole blood–derived platelets should have been passively reported to the FDA between 2004 and 2008 if transfusion of platelet pools was indeed associated with a risk of fatal TRALI. Alternatively, the absence of any such fatalities[1] may be due to chance because such reported deaths represent exceedingly rare events. Yet another explanation could be a lack of TRALI awareness and recognition in environments where pooled whole blood–derived platelets are administered—certainly a possibility because TRALI is known to be grossly underrecognized and underreported.[278]

Similarly to TRALI, during the 2004-2008 period—when pooled whole blood–derived platelets were not subjected to bacterial culture but were screened for bacteria by surrogate methods 4.6 times less sensitive than culture[55]—no fatalities from TAS ascribed to the transfusion of pooled whole blood–derived platelets were reported to the US FDA[1] (Fig 13). During this same period, fatalities from TAS attributed to the transfusion of single-donor platelets continued to be reported (Fig 13), despite the fact that these latter components had been cultured for bacteria. The absence of reported deaths from both TAS and TRALI in association with the transfusion of pooled whole blood–derived platelets not subjected to culture supports the hypothesis that pooled whole blood–derived platelets in the United States are likely administered in environments with less monitoring of transfusion reactions and less access to transfusion medicine expertise. If that is the case, the differences in the numbers of passively reported deaths associated with the 2 types of platelet components can be ascribed to the "passive surveillance artifact" described in the section on sources of data and their interpretation.

In this context, the "passive surveillance artifact" that clouds the interpretation of the data passively submitted to the FDA may operate in yet another manner. The publicity associated with the TRALI risk from transfusion of FFP before 2006[11,16] may have led to increased awareness of the risk of TRALI in association with—specifically—FFP transfusion (Fig 5), as opposed to transfusion of other blood components (including both types of platelet components). Now that the FFP problem is regarded as "solved" (after the conversion to male-

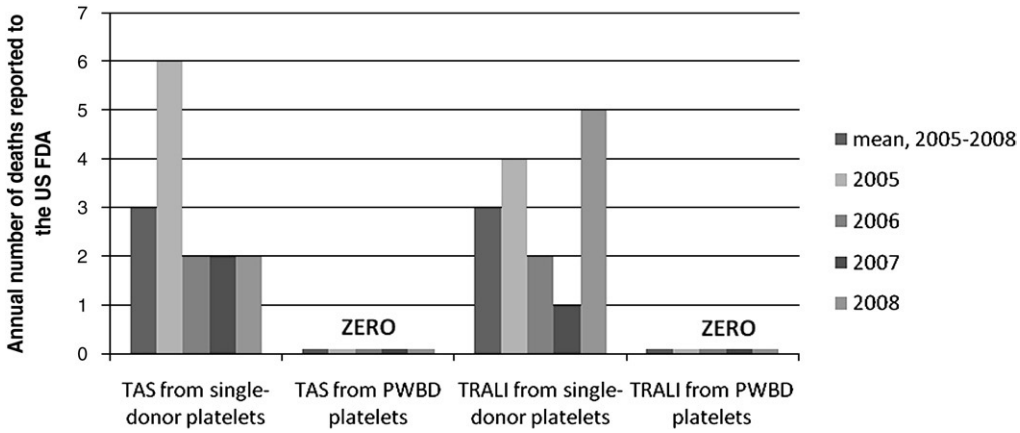

Fig 13. Comparison of the annual number of TAS and TRALI deaths passively reported to the US FDA between 2005 and 2008 in association with single-donor vs pooled whole blood–derived platelets. Abbreviation: PWBD, pooled whole blood–derived.

only FFP) and the question of what to do about single-donor platelets is debated, we could expect an increase in the number of TRALI deaths passively reported to the FDA and attributed specifically to transfusion of single-donor platelets. Such an increase has already occurred in 2008 (with 5 reported deaths;[1] Fig 13), and the number for 2009 may well rise further.

White Blood Cell Reduction of Cellular Blood Components Administered Perioperatively During Cardiac Surgery

The greater part of TA mortality may not derive from the established noninfectious and infectious complications of ABT. If corroborated by future research, the deaths attributed to non–WBC-reduced (vs WBC-reduced) ABT by the RCTs conducted in cardiac surgery[30-32] will represent a far greater number of deaths than the fatalities caused by the many well-recognized transfusion complications. Although 60-day mortality was only a secondary outcome in the cardiac surgery RCT of van de Watering et al,[30] receipt of non–WBC-reduced (compared with WBC-reduced) ABT increased the absolute risk of death by 4.3% (7.8% vs 3.5%) indicating that, for every 23.3 patients receiving non–WBC-reduced (rather than WBC-reduced) ABT, 1 might have died because of the non–WBC-reduced (rather than WBC-reduced) ABT itself.

Allogeneic blood transfusion has not been associated with a specific cause(s) of death in these RCTs,[30-32] and the mechanism(s) by which ABT might cause such an increase in all-cause mortality is not yet understood. Although there is a need for further research to elucidate the mechanism of the apparent increase in mortality in recipients of non–WBC-reduced (compared with WBC-reduced) ABT, we believe that—where excess mortality has been attributed to non–WBC-reduced (compared with WBC-reduced) ABT by RCTs—WBC reduction of cellular blood components should be implemented to prevent such excess deaths. This situation has been reported only in cardiac surgery—a setting apart from other surgical (or medical) settings, in which idiosyncratic effects of ABT could be expected and would not necessarily be generalizable to other settings.[239,240]

Approximately 80% of platelet and 55% of RBC units currently transfused in the United States are WBC reduced.[56] The number of WBC-reduced components declined by 12% between 2004 and 2006 (from 12 to 10.6 million components).[56] The US hospitals use WBC-reduced components either universally or selectively, depending primarily on their geographic location and the practices of the local blood center (which may manufacture only WBC-reduced or both WBC-reduced and non–WBC-reduced cellular blood components). When selective WBC reduction is used, administration of WBC-reduced components to cardiac surgery patients is usually not included among the established indications for WBC reduction.[279] Thus, in some US hospitals, WBC-reduced RBCs are administered routinely to patients whose mortality has not been shown to be affected by WBC reduction, whereas elsewhere cardiac surgery

patients whose mortality has been shown to be improved by WBC reduction may not always receive WBC-reduced components.

To ensure that all cardiac surgery patients receive WBC-reduced cellular blood components, we could either redistribute some of the already manufactured WBC-reduced cellular blood components from US hospitals using universal WBC reduction to the cardiac surgery setting of US hospitals not using universal WBC reduction, or we could increase the overall proportion of the cellular blood components WBC-reduced in the United States. Whether the goal is accomplished through a redistribution or a net increase in manufactured WBC-reduced components, we believe that all cellular blood components transfused in cardiac surgery in the United States should be WBC-reduced based on the existing evidence.[239,240] For US hospitals using selective WBC reduction, this safety enhancement can be accomplished by adding cardiac surgery to the 3 established indications for WBC reduction, namely, prevention of HLA alloimmunization and refractoriness to random-donor platelet transfusions, prevention of transmission of CMV, and prevention of febrile, nonhemolytic transfusion reactions.

Pathogen Reduction of Platelet and Plasma Components

So many agents can potentially threaten blood safety[29] that blood establishments cannot easily keep up with implementing safety measures in response to each one of them. Rather than this "agent-by-agent" approach, there should be a more all-encompassing "proactive" approach to blood safety that would address most transfusion-transmitted pathogens such as the use of PR by nucleic acid intercalating agents (ie, psoralens and riboflavin) in the presence of ultraviolet light.[23,280-282] These technologies bind the photosensitizing agents to the nucleic acids of pathogens and inactivate them, while permitting the nucleic acid–free constituents of donor blood (plasma proteins, platelets, and RBCs) to continue to function.[280] Thus, these technologies can eliminate most of the residual risks of bacteria as well as the risks associated with a long list of transfusion-transmitted pathogens for which the blood supply is not screened (eg, *Plasmodium* sp, *Babesia* sp, and so on). Perhaps more important, these technologies offer potential, preemptive protection against the next potentially lethal transfusion-transmitted agent that will inevitably emerge in the future, replicating the experience with HIV or WNV.[23]

Such technologies are currently available for platelets and FFP, have an acceptable safety profile,[283-288] and have already been licensed for use in some Western European countries.[29] Although the safety improvement they confer is widely acknowledged, there is debate as to whether PR for all platelets and plasma should be introduced before suitable PR technologies also become available for RBCs. The contribution of PR to safety can be only suboptimal if PR technology cannot simultaneously also be applied to RBCs, with the latter continuing to transmit pathogens to transfusion recipients. Also, until there is a comprehensive system of PR that also encompasses RBCs, permitting various cost-savings from the possible discontinuation of other safety measures, the cost of PR is bound to be incremental and substantial.[289] However, many patients receive repeated platelet transfusions only intermittently accompanied by RBC transfusions, and—however medically inappropriate[241]—platelet and/or FFP transfusions are often given "prophylactically" to patients scheduled to undergo bedside or invasive procedures because of a moderately lowered platelet count or moderately elevated INR.

Pathogen reduction likely will not protect recipients from all future transfusion-transmitted pathogens. It is ineffective against pathologic prions (ie, the vCJD agent), intracellular pathogens, spore-forming bacteria, nonenveloped viruses, and viruses present in exceedingly high concentrations in blood. Another downside is that it causes cellular and functional protein losses, thus, reducing the therapeutic efficacy of blood components, necessitating the transfusion of greater volumes of blood and exposing patients to more donors, thereby, increasing the risk of transmission of agents not inactivated by PR. Despite this plausible prediction, however, RBC and platelet use has been reported to remain the same before and after the introduction of a pathogen inactivation system in 2 Western European countries.[290,291] Also, there was no increase in the platelet transfusion needs of patients receiving platelets treated with riboflavin-based PR technologies compared with subjects in the untreated arm of the one reported trial.[292]

Potential toxic effects of the candidate PR systems have been examined in many dimensions,

including acute, subacute, and chronic toxicity; blood component incompatibility; genotoxicity; carcinogenicity; and impact on reproduction and development. Although no evidence of such adverse effects has hitherto been adduced, the clinical events of interest are rare and may have very long latent periods before they become recognized, especially regarding mutagenicity and carcinogenicity.[29]

These concerns about possible long-term toxicities of PR technologies cannot be alleviated until long-term outcomes are reported from the Western European countries in which PR technologies have been already (at least partly) introduced into clinical practice. These concerns must be considered, however, in the context of the possible additional short-term benefits from PR technologies. Unlike WBC reduction filters that leave up to 5×10^6 residual WBCs behind in each WBC-reduced blood component, PR technologies eliminate all allogeneic WBCs. In this way, they can prevent the rare deaths from TA-GVHD that can occur in patients given unirradiated components by mistake or because they do not have a recognized indication for irradiation.[281]

Furthermore, an RCT of the efficacy and safety of platelets that had undergone PR demonstrated a trend toward reduced mortality in the patients supported with treated platelets, concerning especially the mortality from ALI.[293] Acute lung injury is a significant cause of morbidity and mortality in recipients of allogeneic bone marrow transplants—a setting in which ALI may account for up to 25% to 50% of all deaths. If PR truly renders platelets less apt to cause ALI in transfusion recipients, plausible explanations for this effect would include reduction in cytokine synthesis and/or antigen presentation, owing to the absence of WBCs in the treated products.

Pathogen reduction processes can be applied to either single-unit plasma units or plasma pools. Thus, there are now 4 licensed technologies for PR of plasma in Europe. Most clinical experience (>6 million U transfused) has hitherto been accrued with pooled plasma subjected to solvent-detergent treatment.[288] Pooling of 500 to 2500 plasma donations has the disadvantage that one single plasma unit can contaminate the whole pool. However, this drawback can be offset by several advantages, including the virtual elimination of TRALI attributable to WBC antibodies, a significant reduction in the incidence of allergic reactions owing to dilution of allergens, and standardization of the product for therapeutic use in its coagulation factor content (because individual plasma donors contributing to the pool have a wide range of coagulation factor levels, varying between 50% and 200%).[288,294,295]

In TRALI reduction, solvent-detergent–treated pooled plasma—which is currently used to meet virtually all the plasma needs of Norway and Ireland and has contributed 464 582 (compared with 650 781 for FFP) transfused units of plasma in France between 2003 and 2006[288]—needs to be compared with the male-only FFP currently being used in North America. The solvent-detergent–treated pooled plasma should be as effective as male-only FFP in reducing the risk of TRALI because the manufacturing process dilutes, and possibly neutralizes, WBC antibodies.[295] In fact, no reports of TRALI have appeared from Western European countries using solvent-detergent–treated pooled plasma. In particular, during the aforementioned period (2003-2006),[288] after the French hemovigilance system started appropriate monitoring for TRALI, there were 14 (9 probable or certain and 5 possible) cases of TRALI in association with transfusion of FFP (1 per 25 346 U), as compared with no case of TRALI in association with transfusion of solvent-detergent–treated pooled plasma.[296,297]

Furthermore, although for most TTIs that would occur in association with the use of solvent-detergent–treated pooled plasma, a single contaminated unit might contaminate the entire pool, at least in theory, there can be situations in which pooling offers advantages for preventing transmission of TTIs.[298] Although there are no data on the risk of vCJD infectivity of solvent-detergent–treated pooled plasma, if anything, the low titer of prion infectivity in the blood of an infected individual (approximately 10 infectious U/mL) would be greatly diluted by the thousands of units of plasma in the plasma pool. Subsequent manufacturing processes should also remove prions from the final product.[298]

The solvent-detergent treatment of pooled plasma results in appreciable losses of protein S, antitrypsin, and antiplasmin.[288] These losses have generated concern when the product is used in patients with hyperfibrinolysis (such as occurs during the reperfusion stage of liver transplantation). Because of a cluster of deaths in such patients in the United

States,[299] solvent-detergent–treated pooled plasma use fell out of favor in North America. The current manufacturing process used in Europe is different, resulting in reduced—albeit still appreciable—loss of these 3 proteins. Nonetheless, the Irish—who almost exclusively use solvent-detergent–treated pooled plasma for the plasma needs of their transfusion recipients—do not use this product for patients undergoing liver transplantation.[300]

Because it cannot be predicted when the next major transfusion-transmitted pathogen will emerge, we believe that PR technologies for platelets and plasma should be implemented by the transfusion medicine community when they are licensed rather than waiting for PR technologies for RBCs to also be developed, perhaps in the next 5 to 10 years.[282] If the next agent to emerge is an enveloped virus (such as HIV, HBV, HCV, or WNV), a potential future HIV-like epidemic of a fatal transfusion-transmitted infection can be averted. Several safety measures (including bacterial detection in platelets and screening for antibody to *Trypanosoma cruzi*) could also potentially be discontinued when PR is universally introduced for all blood products. At the same time, however, we recognize the potential for the debate over PR to have a negative effect on safety, by producing a situation of continued inaction vis-à-vis addressing the (residual) risk of bacteria in platelets/TAS and other known infectious risks through the other interventions discussed in this review.

CONCLUSIONS

Four of the 6 strategies proposed here (evidence-based transfusion guidelines, avoidance of pooled whole blood–derived platelets, avoidance of female FFP and of plateletpheresis donors who have a history of pregnancy and have not tested negative for WBC antibodies, as well as WBC reduction of cellular blood components administered in cardiac surgery) have already been—at least partly—implemented in the United States. Strategies that have already been introduced, however, have not been adopted universally or uniformly, and the benefit that they can confer in preventing ABT-related deaths has not yet been fully realized. For example, 12.5% of therapeutic platelet doses continue to be provided as pooled whole blood–derived platelets[56]; also, female plateletpheresis donors with a history of pregnancy who have not been tested for WBC antibodies continue to be used by most blood centers, and debated approaches to the handling of such donors range from testing for WBC antibodies all women with a history of pregnancy to testing only women with 4 or more pregnancies.

In conclusion, allogeneic blood transfusions can be lifesaving for bleeding patients, but in patients who are not bleeding, we should require positive evidence of benefit before exposing any patient to the risks of transfusion. Transfusion should never be considered inherently "safe" nor administered prophylactically without evidence of its efficacy to improve oxygen consumption by tissues or prevent hemorrhage. Although acknowledging that a "zero" risk is not an attainable goal, discussions of recent progress in blood safety should not detract attention from the fact that more needs to be done, or lessen the sense of urgency for us to continue to strive for an "as low as reasonably achievable"[301] risk. In this spirit, we have proposed 6 strategies for further risk reduction that—with the exception of PR technologies for plasma and platelets that are not yet available in the United States—are, in our opinion, ripe for implementation.

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