Utility of cross-matched platelet transfusions in patients with hypoproliferative thrombocytopenia: a systematic review

Ralph R. Vassallo,[1] Mark Fung,[2] Paolo Rebulla,[3] Rene Duquesnoy,[4] Chee Loong Saw,[5] Sherrill J. Slichter,[6] Susano Tanael,[7] and Nadine Shehata[7,8,9] for the International Collaboration for Guideline Development, Implementation and Evaluation for Transfusion Therapies. Collaborators (22)

BACKGROUND: Multiply transfused hypoproliferative thrombocytopenic (HT) patients with alloimmune transfusion refractoriness require specially selected platelets (PLTs). Cross-matching apheresis PLTs is a popular support option, avoiding requirements for large panels of typed donors for HLA-based selection. We undertook a systematic review of the utility of various cross-matching techniques on mortality reduction, prevention of hemorrhage, alloimmunization and refractoriness, and improvement in PLT utilization or count increments.
STUDY DESIGN AND METHODS: A systematic review to December 2012 was conducted of MEDLINE, EMBASE, and Cochrane databases along with a bibliographic search of pertinent references.
RESULTS: Of 146 retrieved citations, 20 met inclusion criteria. Eleven more were chosen from bibliographies, describing 29 unique cohorts. All but five enrolled transfusion-refractory, predominantly alloimmunized patients. Cross-match impact on mortality and hemorrhage could not be assessed from these studies. Two studies demonstrated durable corrected count increments and/or breadth of alloimmunization throughout cross-match support; none addressed development or persistence of refractoriness. In alloimmunized refractory patients and nonrefractory cohorts with greater than 25% alloimmunization, higher increments were seen with cross-match–compatible PLTs than incompatible or un–cross-matched units. In two nonrefractory, nonalloimmunized cohorts, the lack of utility of cross-match was reflected by test sensitivity of less than 20%. Comparison of cross-matched PLT success with that of HLA-identical units revealed inferior success rates for the former in one study and equivalent rates in another. No trend was observed regarding relative utility of the various commonly employed techniques.
CONCLUSION: Cross-matched PLTs are useful in increasing PLT counts in alloimmunized, transfusion-refractory HT patients, but data about their impact on hemorrhage and mortality are lacking.

BACKGROUND

In multiply transfused patients with hematologic disease or malignancy, unexpectedly low count increments are seen after 30% to 50% of platelet (PLT) transfusions, while 25% to 70% of patients experience at least one poor

ABBREVIATIONS: HT = hypoproliferative thrombocytopenia; LCT = lymphocytotoxicity test; LR = leukoreduced; NPV = negative predictive value; PPR(s) = percent PLT recovery(-ies); PPV(s) = positive predictive value(s); PRA = percent reactive antibody; PRAT = platelet radioactive antiglobulin test; PSIFT = platelet suspension immunofluorescence test; RDP(s) = random-donor platelet(s); SPRCA = solid-phase RBC adherence assay.

From the [1]American Red Cross Blood Services, Penn-Jersey Region, Philadelphia, Pennsylvania; the [2]Department of Pathology and Laboratory Medicine, University of Vermont and Fletcher Allen Health Care, Burlington, Vermont; the [3]Center of Transfusion Medicine, Cellular Therapy and Cryobiology, Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; the [4]Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; the [5]HLA Laboratory, Haematology Division, McGill University Health Centre, Montreal, Quebec, Canada; the [6]Puget Sound Blood Center and the University of Washington School of Medicine, Seattle, Washington; [7]Canadian Blood Services, the [8]Departments of Medicine, Obstetric Medicine, Laboratory Medicine and Pathobiology, Mount Sinai Hospital, University of Toronto, and the [9]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada.

Address reprint requests to: Ralph R. Vassallo, MD, American Red Cross Blood Services, Penn-Jersey Region, 700 Spring Garden Street, Philadelphia, PA 19123; e-mail: ralph.vassallo@redcross.org.

Funding for this systematic review was provided by Canadian Blood Services.

Received for publication April 4, 2013; revision received May 30, 2013, and accepted June 28, 2013.

doi:10.1111/trf.12395

TRANSFUSION 2014;54:1180-1191.

increment.[1] True PLT transfusion refractoriness, however, entails repeated inappropriately low count increments. Patients with hypoproliferative thrombocytopenia (HT) are at particular risk for serial count increment failures due to comorbid clinical conditions and medical interventions associated with poor PLT recovery and survival.[2] Many of these conditions are associated with nonimmune PLT destruction or sequestration (e.g., fever, severe infection, hemorrhage, disseminated intravascular coagulation, hematopoietic stem cell transplantation, amphotericin B use, and splenomegaly). An addressable cause of PLT destruction is the development of alloantibodies directed against antigens expressed on PLTs, usually human leukocyte antigens (HLA) and sometimes, human PLT antigens (HPA). Historically, depending on the duration of support and availability of leukoreduced (LR) cellular components, 10% to 100% of HT patients produced alloantibodies, most of which did not cause transfusion refractoriness.[3,4] More recent data in leukemia patients and hematopoietic stem cell recipients transfused exclusively with LR products show that 4% to 8% develop alloimmune refractoriness.[3,4] Most alloantibodies are directed at HLA Class I antigens, so support begins either with PLTs whose HLA determinants are matched to the recipient's or with those deemed compatible by cross-match testing.[5]

Apheresis PLT donors who are functionally HLA identical at all four HLA-A and HLA-B loci were traditionally preferred. This approach is costly because of the requirement for large panels of typed donors and results in delays during patient HLA typing and donor recruitment. Additionally, as many as 20% to 30% of functionally HLA-identical units still resulted in inadequate increments.[6] Further, since identical matches were frequently unavailable, units selectively mismatched at one or more loci were more often provided, which were even more likely to result in inadequate increments.[7] A newer approach involves the use of PLTs negative for the HLA Class I antigens to which the patients are immunized. This demands quite sensitive recipient antibody identification techniques to search for functionally compatible units, but requires smaller panels of typed donors.[8] Anecdotal experience and preliminary studies suggest that antigen-negative units may be as successful as HLA-identical units.[9]

Cross-matching techniques were developed in hopes of improving transfusion success rates and to circumvent the need for large panels of HLA-typed donors. Initially, donor lymphocyte cross-matching by cytotoxic or immunofluorescent antiglobulin techniques identified potentially HLA-compatible individuals who had recently donated PLTs (and provided a whole blood specimen) or were willing to donate after testing of stored panel lymphocytes. While not dramatically impacting transfusion failure rates, cross-matching greatly improved the availability of PLTs. Recognizing the failure of lymphocyte testing to identify HPA and clinically significant ABO blood group antibodies, testing for PLT-associated immunoglobulin G was first added to, then supplanted, lymphocyte testing in the United States. In these assays, donors' PLTs are incubated with recipient serum. Bound immunoglobulin is then detected by antiglobulins (or staphylococcal protein A) labeled with radionuclides, enzymes, or fluorescent compounds. Antiglobulins may also be bound to indicator red blood cells (RBCs) or latex beads and agglutination assessed. Earlier PLT cross-matching techniques measuring aggregation, PLT granule release, or membrane lipid responses to recipient plasma were insufficiently reliable and never widely employed.[10]

Cross-matching is a popular support option for HT patients in hospitals without access to large panels of HLA-typed apheresis donors. Commercial and locally developed cross-match assays have been used to identify alloimmunization in transfusion-refractory individuals as well as to choose potentially compatible units. Many techniques have been studied in a variety of settings, from highly selected transfusion-refractory patients with few or none of the clinical conditions known to blunt transfusion response, to randomly selected patients, some of whom may not even have been refractory. In these studies, refractoriness has been variably defined, and post-transfusion counts have not been consistently reported both at 10 to 120 minutes and at 16 to 24 hours. Immune PLT destruction (including autoimmunity and drug-induced PLT antibodies), brisk hemorrhage, and splenic sequestration appear to have the greatest effect on 10 to 120-minutes-posttransfusion PLT recovery.[11] Most nonimmune conditions have smaller effects initially, but accelerate PLT consumption, resulting in poor 16- to 24-hour counts. Care must be paid to these variables in reported studies to better interpret the effectiveness of cross-matching in various settings. Because of the range of available support alternatives, we chose to investigate the evidence for the utility of cross-matching in patients with HT. A systematic review was undertaken, focusing on reduction in mortality or the frequency and/or severity of hemorrhage and secondarily, improvement of post-transfusion increments, reduction of PLT utilization, and prevention of HLA alloimmunization or transfusion refractoriness.

MATERIALS AND METHODS

Information sources and search

A systematic search, with the assistance of library information specialists, of the electronic databases MEDLINE, EMBASE, and Cochrane Library from 1948 to September 23, 2011 (later updated to December 18, 2012), was conducted, including a bibliographical search. The text words and search strategy are shown in Appendix S1 (available as

supporting information in the online version of this paper).

Study selection

Three authors (MF, NS, RV) independently assessed the citations to identify studies that met the following inclusion criteria: 1) was an original study with transfusion of cross-matched PLTs, 2) included 10 or more individuals with HT, 3) included any of the two primary outcomes (hemorrhage, mortality) and/or four secondary outcomes (PLT increment, PLT utilization, refractoriness, HLA alloimmunization), and 4) was published in English. We excluded studies if they were case reports, letters, or abstracts.

If there was disagreement regarding inclusion, the full-text article underwent independent assessment. Disagreements for inclusion were resolved by consensus for all articles.

Data collection process and data items

Three reviewers (NS, ST, RV) independently extracted data from the included reports to the tables. Data extracted from each of the studies included: 1) study characteristics (publication year, country, single vs. multiple sites, patient population and size, PLT products, and cross-match techniques); 2) quality of individual studies; 3) outcomes of interest (mortality, hemorrhage, PLT increment, PLT utilization, HLA alloimmunization, and PLT refractoriness); 4) definition of successful transfusion response; 5) percentage of negative cross-matches obtained and transfused; and 6) performance estimates—sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy. Estimates were computed if they were not directly reported in the paper.

Assessment of study quality

Quality assessment was based on a checklist that included assessment of the appropriateness of the sample source, sample method, sample size determination, definition of eligibility criteria, definition of outcomes assessment of missing data, and analysis of confounding factors.[12] We also assessed the quality of diagnostic accuracy studies using a checklist of items, Standards for the Reporting of Diagnostic Accuracy Studies (STARD).[13]

Method of analysis

This is a qualitative report. Meta-analysis was not conducted because there was considerable heterogeneity in the measurement of study outcomes and performance estimates.

RESULTS

Study selection

The literature search identified a total of 146 potentially relevant citations. Of these, 126 were excluded because they did not fulfill eligibility criteria. The full-text articles of the remaining 20 citations that met inclusion criteria were retrieved.[7,8,10,14-30] A search of bibliographies identified an additional 11 references[31-41] for a total of 31 reports. Two papers described a previously reported patient cohort, either expanding the scope of variables studied[26] or providing additional analysis of test characteristics.[17] There were thus a total of 29 discrete patient cohorts described.

Ten prospective and 13 retrospective studies were identified (Table S1, available as supporting information in the online version of this paper). Six of the 29 studies were grouped as prospective or retrospective if some portions of the study were conducted prospectively and others retrospectively or if the nature of the study could not be determined.[7,30,38-41] Of these 29 studies, 26 directly reported the diagnostic accuracy of cross-matching or these values could be derived from data provided in charts or narrative study results. A flow diagram of study selection is shown in Fig. 1.

Characteristics and quality of the studies

Seventeen of the 29 study cohorts (Table S1) were from the United States; four were from Canada; three were from the Netherlands; and one each from China, Egypt, Germany, Italy, and Norway. Of the 21 studies reporting the number of participating sites, 17 (81%) were from single institutions. Twelve studies enrolling a total of 501 patients did not specifically report the age of their participants (Table S1). The patient population was largely adult in the remaining studies. Seven exclusively enrolled adult patients, a total of 697 individuals (Table S1) while five enrolled young patients, but did not indicate how many of the 242 participants were less than 16 years of age.[8,22,31,34,37] Of the five studies specifying the number of children, there were 27 pediatric patients and 150 adults (Table S1). Only five reports were published in or after the year 2000. Ten were conducted in the 1990s, 12 in the 1980s, and two in the 1970s.

Various patient populations were the subject of these 29 studies. In the majority (24), individuals with various HT states known or likely to be refractory to PLT transfusions comprised the study groups (Table S1). Three of these 24 did not report the prevalence of antibodies to HLA and/or HPA in their cohorts.[8,28,35] Seventeen included only participants with demonstrable PLT-reactive antibodies. In three of the 21 studies reporting PLT antibody results, approximately half of participants were alloimmunized.[7,10,19] The remaining five of 29 studies

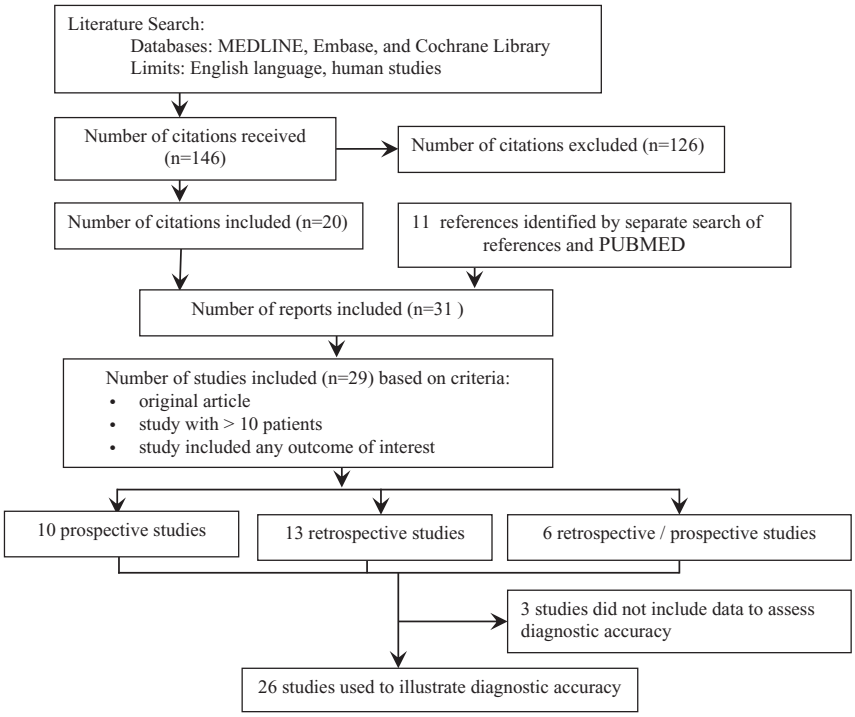

Fig. 1. Flow diagram of the study selection process.

described transfusion outcomes in HT patients not selected for refractoriness. PLT-directed antibodies were demonstrable in 84, 42, 22, approximately 10, and less than 10% of patients in these studies.[14,15,21,23,39]

Fifteen of the 29 studies included only patients selected for the absence of clinical conditions and medical interventions associated with a poor response to transfusion. In all but two,[23,32] enrolled patients were transfusion refractory and in nine of the remaining 13,[18,25,29,31-33,36,37,41] the refractoriness was presumed to be predominantly alloimmune in nature as all patients demonstrated PLT-reactive antibodies. Two additional studies selected patients who manifested refractoriness only in the absence of conditions known to affect transfusion response.[10,24] Cross-matched units were, however, included in the analysis if these conditions were subsequently identified after enrollment.

Transfused PLT products varied (Table S1). Two studies compared a mix of apheresis and whole blood–derived, buffy coat (BC)-random-donor PLTs (RDPs). One used plasma-suspended RDPs,[38] and the other, non-LR PLT additive solution–suspended RDPs.[30] Some patients were transfused exclusively with pooled whole blood–derived PLTs, either pooled PLT-rich plasma RDPs[16,31,32] or LR buffy coat-RDP pools.[21] The remaining 23 studies transfused apheresis products (single-donor PLTs). Only four of the these 23 studies mentioned exclusive use of LR units.[8,14,21,23] The ABO status of cross-matched units was not addressed in seven of the 29 cohorts.[15,16,18,22,30,37,38] Fourteen studies preferentially or exclusively transfused ABO-compatible or ABO-identical units, while eight reports described outcomes for non-ABO selected units.

The PLT count increment was the most commonly reported outcome, but the methods of reporting varied (Table 1). Studies reported mean corrected count increments (CCIs), percent PLT recoveries (PPRs), and/or the percentage of successful transfusions using different success thresholds. Only one study reported intertransfusion intervals.[30] Two studies' primary focus was to compare the utility of cross-matching and HLA selection methods.[7,8]

Few studies clearly described the source of the population sample (12), sampling methods (8), eligibility criteria (15), analysis of potential confounding factors (4), or quality control (14). The sample size was not predetermined in any study and outcome assessment was not blinded (Table S2, available as supporting information in the online version of this paper).

We were able to extract data from 26 studies to assess the diagnostic accuracy of the assays used for cross-matching PLTs (Table S3, available as supporting information in the online version of this paper). Statistical uncertainty of performance estimates as well as indeterminate results, missing responses, or outliers, were generally not reported. Test reproducibility and coefficients of variation were infrequently described. Of the 17 studies evaluating multiple cross-matching techniques, only four provided data on concordance among the various assays.[21,23,25,31]

Outcomes

Of the 1620 patients enrolled in the 29 studies, 1111 received evaluable transfusions, with sample sizes ranging from 10 to 114 patients (mean, 38; median, 32; Table 1). Mortality was only reported by Rebulla and colleagues[30] and rigorously assessed just for the 40 patients who received cross-matched PLTs. Hemorrhage was not systematically assessed in any of the studies, but a World Health Organization (WHO) Grade 4 bleed was reported in one of 18[30] and one of 66[20] patients who received cross-matched units.

Stability of the breadth of anti-PLT alloimmunization was specifically addressed in three studies.[8,20,22] Two studies conducted in refractory patients did not demonstrate a significant reduction in transfusion response or increase in the proportion of incompatible units throughout cross-matched PLT support.[20,22] The third study noted

TABLE 1. Outcomes of studies

First author, year	Sample size	Mortality/ hemorrhage	Refractoriness/HLA alloimmunization	PLT increment
Sayed, 2011[14]	39 (13 pediatric)	NS	NS	58% PSIFT XM compatibles had 1-hr CCI ≥ 4500 or 18- to 24-hr CCI ≥ 2500 vs. 12% un–cross-matched (p = 0.02 for all patients); in adults 51% PSIFT XM compatibles vs. 17% un–cross-matched (p = 0.143); in children 73% PSIFT XM compatibles vs. 0% un–cross-matched (p = 0.041). 45% PSIFT XM compatibles had 1-hr CCI ≥ 4500 or 18- to 24-hr CCI ≥ 2500 with clinical factors vs. 86% PSIFT XM compatibles without clinical factors (p = 0.008). 29% PSIFT XM compatibles had 1-hr CCI ≥ 4500 or 18- to 24-hr CCI ≥ 2500 with anti-HLA vs. 74% PSIFT XM compatible without anti-HLA (p = 0.001).
Petz, 2000[8]	111 (pediatric number NS)	NS	14.3% of 35 patients with serial PRAs broadened, 31.4% decreased	Adjusted mean PPR 20.8% for HLA-identical units vs. 23.4% XM vs. 24.1% antigen negative vs. 14.9% random (BX/C HLA matches considered random); XM, antigen negative, and HLA identical not significantly different; only XM and antigen negative significantly better than random.
Ogden, 1993[15]	50	NS	NS	Weighted mean LAA XM compatible 1-hr CCI/PPR 11,800/34.6% vs. XM incompatible 1100/3.3%.
O'Connell, 1990[16]	41	NS	NS	Mean ELISA XM compatible 10-min CCI 4300 (range, 0-13,600) vs. SPRCA XM compatible 9500 (range, 0-26,300) vs. un–cross-matched 2100 (range, 0-5600) vs. HLA matched 17,100 (range, 7100-27,200). 30% ELISA XM compatibles had 10-min CCI ≥ 7500 vs. 57% SPRCA XM compatibles. 24% of XMs were compatible by ELISA and 15% were compatible by SPRCA.
Freedman, 1988[31]	26 (pediatric number NS)	NS	NS	Mean PRAT XM compatible 1-hr/24-hr CCI 13,900 ± 12,700/7300 ± 6900 vs. LCT XM compatible 12,400 ± 13,400/5300 ± 7500 vs. PRAT XM incompatible. 5700 ± 7800/2100 ± 4100 vs. LCT XM incompatible 4800 ± 8700/2200 ± 4100 (p = NS for PRAT vs. LCT); un–cross-matched 1-hr CCI 5900 ± 80/2600 ± 1100.
Kickler, 1988[18]	11	NS	NS	Mean PRAT XM-compatible 1-hr/18- to 24-hr CCIs 18,370 ± 4670/7318 ± 3317 vs. XM incompatible 2538 ± 3508/227 ± 657 (p < 0.001).
Rachel, 1988[19]	28/87 evaluable (17 without nonimmune factors)	NS	NS	Mean SPRCA XM-compatible 1-hr CCI 16,300 ± 9600 vs. incompatible 4100 ± 5100; CCIs 19,200 ± 8000 for compatible vs. 3800 ± 3100 for incompatible in subgroup without nonimmune factors. 77% SPRCA XM compatible had 1-hr CCI ≥ 10,000; 95% for subset without clinical factors. Compatible XMs found for 96% nonalloimmunized, 31% moderately alloimmunized, and 4% heavily alloimmunized.
Freedman, 1984[32]	29	NS	NS	Mean PRAT XM-compatible 24-hr CCI 17,789 ± 2010 vs. incompatible 1195 ± 560 vs. un-XM 4424 ± 970 (p < 0.001). 92% PRAT XM compatible had 24-hr CCI ≥ 4500 vs. 14% PRAT XM incompatible vs. 36% un-XM.
Kakaiya, 1984[10]	32 (two pediatric)	NS	NS	52% ELISA compatible had 24-hr CCI ≥ 4500 vs. 52% PSIFT vs. 41% LCT; 25% ELISA incompatibles had 24-hr CCI ≥ 4500 vs. 30% PSIFT vs. 0% LCT.
Brand, 1978[33]	15	NS	NA	90% PSIFT XM compatible had 20-hr CCI ≥ 4500 vs. 0% PSIFT XM incompatible in highly selected population receiving HLA-selected, LCT-XM–compatible units. Addition of PSIFT to HLA selection and LCT-XM compatibility reduced failures from 35% to 7%.
Wiita, 2012[20]	71 (66 received XM units)	n = 1 with WHO Grade IV pulmonary hemorrhage	XM % incompatibility mean: 58.6% at initiation vs. 55.3% at final XM, p = ns; slope of least-squares regression lines of longitudinal % of incompatible XMs centered around zero.	Mean CCI of XMs 7000 ± 7900 vs. random units 710 ± 2700 (p < 0.001); 41% XMs had 1-hr CCI ≥ 7500
			Mean CCI response to XM units unchanged.	Weak correlation between CCI and XM reactivity (Pearson r = 0.08); 45% with XM incompatibility rates ≥ 66% had at least one subsequent XM with no compatible units.
Levin, 2004[21]	95	NS	NS	60%/64% PSIFT XM compatible had 1-hr PPR ≥ 20%/16-hr PPR ≥ 10% vs. 46%/54% of PSIFT XM incompatible (p = NS). PSIFT XM incompatibility unable to predict poor recovery, even in subset without splenomegaly or receiving >3-day-old units (nor did in vivo PSIFT XM incompatibility).
Gelb, 1997[22]	66 (pediatric number NS)	NS	Slope of least-squares regression line of longitudinal XM unit CCIs centered around zero	Mean SPRCA XM-compatible 1- to 4-hr CCI 9800 (range, 600-31,200) vs. non-XM 1800 (range, 3900-7400; p < 0.0001). 51% XM compatibles had 1- to 4-hr CCI ≥ 7500.
Kohler, 1996[23]	45	NS	NS	93% LCT compatibles had 1-hr CCI ≥ 7500 or 18- to 24-hr CCI ≥ 4500 vs. 88% LCT incompatibles, 94% LIFT compatible vs. 81% LIFT incompatible, 97% PSIFT compatible vs. 61% PSIFT incompatible; only PSIFT significantly predictive of transfusion outcome.

TABLE 1. *Continued*

First author, year	Sample size	Mortality/ hemorrhage	Refractoriness/HLA alloimmunization	PLT increment
Sintnicolaas, 1996[24]	30	NS	NS	75% PSIFT XM compatible had 1-hr PPR ≥ 20% vs. 45% PSIFT XM incompatible ($p = 0.004$). PSIFT compatibility predictive value preserved when nonimmunologic factors present, but rate of 1-hr PPR ≥ 20% fell from 81% to 50%. ABO incompatibility associated with higher rate of PSIFT incompatibility (64% vs. 14%, $p < 0.001$), and predictive value of PSIFT disappeared (70% success with compatible vs. 50% incompatible, $p = 0.31$).
Gates, 1994[25]	17	NS	NS	Mean PSIFT XM compatible 1-hr CCI was 9195 vs. PSIFT XM incompatible 2269 ($p < 0.05$); assay performance improved with PRA > 35%.
Chow, 1991[34] and 1992[26]	24 (pediatric number NS)	NS	NS	Mean LCT XM-compatible 18-hr CCI 17,710 vs. XM incompatible 700 vs. un-XM 2390 ($p < 0.05$ compatible vs. incompatible or un–cross-matched). Mean 18-hr CCI of XM-compatible units 22,970 ± 4070 for A/BU/BX matches, 15,100 ± 1970 for C/D matches, and 14,500 ± 2040 for random matches (p = NS). Median CCI for LCT XM compatible, ABO identical ~12,500/μL vs. ~13,600 plasma incompatible vs. ~16,500 PLT incompatible ($p = 0.44$).
McFarland, 1987[35]	22	NS	NS	69%/50% PRAT XM compatible had 1-hr PPR ≥ 43.3%/24-hr PPR ≥ 38% vs. 21%/0% PRAT XM incompatibles.
Heal, 1987[27]	51 (three pediatric)	NS	NS	57% ELISA XM compatibles had 1- to 4-hr PPR ≥ 7500 vs. 33% ELISA XM incompatible ($p < 0.001$). 74% A/BU matched ELISA XM compatible had 1- to 4-hr PPR ≥ 7500 vs. 62% BX vs. 51% C ($p = 0.03$ for A/BU vs. C). 66% ABO identical ELISA XM compatible had 1- to 4-hr PPR ≥ 7500 vs. 54% plasma incompatible vs. 43% PLT incompatible ($p = 0.01$ for identical vs. PLT incompatible). Median A/BU matched ELISA XM compatible 1- to 4-hr CCI was 13,300 vs. 9700 BX vs. 7800 C ($p < 0.05$ for A/BU vs. C). Median ABO identical ELISA XM compatible 1- to 4-hr CCI 10,000 vs. 8200 ABO plasma incompatible vs. 5900 ABO PLT incompatible ($p < 0.05$).
Kickler, 1985[36]	42	NS	NA	1-hr/18- to 24-hr CCI failures of A/BU matches were 20%/24% vs. BX 41%/69% vs. C 37%/50% vs. D 36%/57%; 1-hr PRAT NPV was 90%-94% for all match grades.
Ware, 1984[37]	15 (pediatric number NS)	NS	NS	Tests concordant 68% of time; with PSIFT and PRAT incompatible, mean 1-hr CCI 2341 ± 3268 and 100% had 1-hr CCI < 10,000; with PSIFT and PRAT compatible, mean 1-hr CCI 17,191 ± 7275 and 93% had 1-hr CCI ≥ 10,000; mean 1-hr CCI 12,248 ± 8488 for discordant tests; CCI not correlated with HLA grade.
Yam, 1984[28]	18	NS	NS	80% of PRAT XM compatible had 1-hr PPR ≥ 20% vs. 11% of incompatible.
Kickler, 1983[29]	19 (seven pediatric patients)	NS	NS	Mean PRAT XM compatible 1-hr/20-hr CCIs 17,570 ± 7003/8722 ± 3143 vs. 4231 ± 4100/571 ± 1286 PRAT XM incompatible ($p < 0.005$ for 1-hr CCIs).
Rebulla, 2004[30]	480 (40 refractory)	1/18 refractory patients receiving XM died from hemorrhage vs. 6/71 of nonrefractory patients 45% of refractory vs. 33% of nonrefractory patients died during follow-up	NS	68% SPRCA XM compatible had 1-hr increment ≥10,000/μL. Mean SPRCA XM-compatible pretransfusion, 1-hr, and 24-hr counts were 7500 ± 5500, 32,000 ± 21,000, and 16,800 ± 15,500/μL vs. random 7000 ± 8600, 15,900 ± 16,100, and 9600 ± 12,800/μL ($p < 0.05$ for posttransfusion values). Lower posttransfusion counts noted in 18 patients with clinical factors than the 22 without. Median random unit intertransfusion interval was 1 day/2 days (with/without nonimmune factors) vs. XM compatible 2 days/3 days (with/without nonimmune factors).
Skogen, 1995[38]	Eight refractory alloimmunized; 23 nonalloimmunized, without nonimmune factors; 13 nonalloimmunized, with nonimmune factors	NS	NS	Nonrefractory, nonalloimmunized had no positive XMs; % of 1-hr CCI ≥ 7500 for refractory patients was 94% for PSIFT XM compatible vs. 13% for XM incompatible.
Moroff, 1992[7]	78 (five patients excluded: no compatible XMs could be found)	NS	NS	% 1-hr CCI ≥ 7500 not different (54% HLA vs. 48% XM), but % 24-hr CCI ≥ 4500 were (42% HLA vs. 23% XM, $p < 0.05$); 73% A/BU matches had 1-hr CCI ≥ 7500 vs. 48% XM compatible and 41% HLA-selected BX, C, and D matches ($p < 0.05$).
Lane, 1990[39]	36 (two < 5 years old)	NS	NS	Mean SPRCA XM-compatible 18-hr CCI was 13,300, not significantly different from untested transfusions; negative SPRCA XM was the only significant factor affecting CCI (not ABO, HLA match grade, or anti-LCT; $p < 0.05$).
Bowen, 1986[40]	13	NS	NS	% 1- to 4-hr CCI ≥ 4500 and 1- to 4-hr PPR > 13.3% was 90% for LCT XM compatible vs. 17% XM incompatible, 84% for PIFT XM compatible vs. 59% XM incompatible, 80% for ELISA XM compatible vs. 67% XM incompatible.
Filip, 1976[41]	10	NS	NS	% 24-hr PPR ≥ 13.3% was 83% for LCT XM compatible vs. 28% XM incompatible, 53% for serotonin release XM compatible vs. 33% XM incompatible, 57% for PF3 expression XM compatible vs. 36% XM incompatible, 61% for aggregation XM compatible vs. 50% XM incompatible.

XM = cross-match.

that few patients (14.3%) broadened their percent reactive antibody (PRA) from 0%-10% to 10%-80% or from 10%-80% to more than 80% when serial values were measured.[8] These data were not limited to cross-match recipients; however, so the role of this support modality cannot be evaluated.

The development or persistence of refractoriness during cross-match support was not addressed. One study reported median intertransfusion intervals for cross-matched units versus preceding randomly chosen units (2 days and 1 day, respectively).[30]

Significantly higher count increments were described for cross-match–compatible versus cross-match–incompatible PLTs in alloimmunized, refractory patients,[18,24,25,27,29,32,34] and for cross-match–compatible versus un–cross-matched PLTs[8,14,20,22,32,34] (all but one[14] in refractory individuals). Higher increments for cross-match–compatible units versus cross-match–incompatible[19,28,30,33,35,37,38,40,41] or un–cross-matched PLTs[16,31] were also found in other studies but significance was not reported. In nonrefractory patients, three of five studies showed that cross-match–compatible PLTs did not result in significantly higher CCIs or success rates with four of the five assays studied.[21,23,39] Three studies reported CCI success rate comparisons for cross-matched units solely amongst the studied assays[10,36] or against HLA-matched units.[7]

Transfusion of PLTs that were cross-match compatible by dual techniques (the PLT suspension immunofluorescence test [PSIFT] and PLT radioactive antiglobulin test [PRAT]) resulted in nearly uniform transfusion success in one small study (15 patients).[37] Similarly, in another study of 15 patients, addition of PSIFT to lymphocytotoxicity testing (LCT) resulted in markedly improved success rates.[33]

Eleven studies evaluated the role of HLA matching in cross-matched PLT transfusion outcomes.[7,10,26-29,33,35-37,39] Of these, 10 concluded that cross-match techniques had similar predictive ability across all categories of HLA match (identical or one-antigen mismatches within or outside cross-reactive groups) while one concluded that cross-matching and HLA and ABO matching all had independent predictive value for increment success.[27]

Fifteen studies employed PSIFT techniques. Two of four reports of unselected (i.e., not uniformly refractory) thrombocytopenic patients demonstrated higher success rates with cross-matched than un–cross-matched or cross-match–incompatible PLTs.[14,23] The other two studies had low rates of unit incompatibility and thus found no utility to PSIFT cross-matching.[21,38] Six of eight studies in refractory patients reported that success rates or absolute CCIs were higher with cross-match–compatible than cross-match–incompatible units.[24,25,33-35,37]

Of nine studies that reported the utility of LCT cross-matching, two concluded that the test was helpful since cross-match–compatible units resulted in significantly better CCIs than incompatible units.[31,34] Another found that LCT performed better than PSIFT and the enzyme-linked immunosorbent assay (ELISA), but the authors expressed concern that their LCT results were much better than those previously reported.[40] The balance of the studies suggested that LCT was considerably less useful in predicting transfusion outcomes. Three studies noted that LCT performed less well than PRAT-, PSIFT-, or ELISA-based cross-matching.[10,25,35] In unselected, nonrefractory patients, despite very poor sensitivity of the LCT assay, one study found good NPV because of the rarity of incompatible cross-matches.[23] The remaining two studies concluded that LCT was "unsatisfactory."

The PRAT assay was found to be associated with transfusion success in the nine studies that reported its use.[7,18,28,29,31,32,35-37] Three studies observed that the PRAT performed better than LCT, PSIFT, and peroxidase-antiperoxidase testing.[28,35,37]

Of the seven studies that utilized the commercially available Capture-P solid-phase RBC adherence assay (SPRCA) method, five compared count increments of cross-matched units with unmatched units[16,20,22,30,39] or cross-match–incompatible units.[19] Except for one study conducted in nonrefractory patients,[39] each of the six studies reporting count increments or CCIs found cross-matched units to be superior.

Seven studies employed ELISA as a cross-match technique. Three described ELISA cross-match–compatible units as having better CCIs than incompatible units,[10,27,31] one found "good sensitivity" and a high NPV,[40] and the last suggested that SPRCA was superior to ELISA for cross-matching.[16] Only one study in nonrefractory patients reported that ELISA was not predictive of poor transfusion outcomes.[21]

Eight studies evaluated 10 less mainstream assays, which included flow cytometry–based lymphocyte immunofluorescence,[23] latex agglutination,[15] the monoclonal antibody immobilization of PLT antigen assay,[24] PLT adhesion immunofluorescence,[25,38] peroxidase-antiperoxidase,[28] PLT ^{51}Cr release,[35] PLT serotonin release, PLT Factor 3 expression, and PLT Factor 3 aggregation,[41] and most were characterized as equivalent to or less effective than the more commonly employed assays.

Table 2 summarizes data from Table S3, focusing on NPVs in various refractory patient subgroups by cross-match technique. The NPV reflects the percentage of compatible units with "successful" outcomes (variously defined). NPVs are provided only for refractory patients because PLT cross-matching in nonrefractory patients appears to be of relatively low value incompatible reactions occurred not more than 15% of the time.

Table 3 summarizes the available data on PPVs. These values reflect the percentage of incompatible units that result in poor PLT increments. Most assays had PPVs in

TABLE 2. NPVs in refractory patient subgroups by cross-match technique*

	All patients						No nonimmune destructive factors					With factors†		
First author, year	PSIFT	SPRCA	LCT	ELISA	PRAT	LAA	PSIFT	SPRCA	LCT	PRAT	LAA	PSIFT	ELISA	Patient group
Chow, 1991[34]	97		98											100% alloimmunized, refractory
Skogen, 1995[38]	94													100% alloimmunized, refractory
Bowen, 1986[40]	84		90	80										100% alloimmunized, refractory
Rebulla, 2004[30]		68												100% alloimmunized, refractory
Gelb, 1997[22]		51												100% alloimmunized, refractory
Kickler, 1983[29]									77	98				100% alloimmunized, refractory
Kickler, 1985[36]										92				100% alloimmunized, refractory
Kickler, 1988[18]										91				100% alloimmunized, refractory
Brand, 1978[33]							90							100% alloimmunized, refractory
Ware, 1984[37]							72			78				100% alloimmunized, refractory
Gates, 1994[25]							73							100% alloimmunized, refractory
Filip, 1976[41]									71					100% alloimmunized, refractory
O'Connell, 1990[16]								57						100% alloimmunized, refractory
Heal, 1987[27]													57	100% alloimmunized, refractory
Freedman, 1984[32]										92				100% alloimmunized, most refractory
Sintnicolaas, 1996[24]	75						81					50		96% alloimmunized, refractory
Ogden, 1993[15]						84					89			84% alloimmunized, refractory
Wiita, 2012[20]		41												96% alloimmunized, most refractory
Rachel,1988[19]		77						95						60% alloimmunized, most refractory
Kakaiya, 1984[10]	52		41	52										50% alloimmunized, most refractory
Yam, 1984[28]										87				<40% alloimmunized, refractory
McFarland, 1987[35]					54					69				Refractory (% alloimmunized NS)
Technique mean	80	59	76	66	54	84	79	76	74	87	89	50	57	
Overall mean			71						82			54		

* Data are reported as percentages.
† "With factors" indicates subgroup of patients, all of whom have nonimmune PLT-destructive factors.

TABLE 3. PPVs in refractory patient subgroups by cross-match technique*

First author, year	All patients					No nonimmune destructive factors					With factors†		Patient group
	PSIFT	SPRCA	LCT	ELISA	PRAT	LAA	PSIFT	SPRCA	LCT	PRAT	LAA	PSIFT	ELISA	
Chow, 1991[34]	90		100											100% alloimmunized, refractory
Skogen, 1995[38]	87													100% alloimmunized, refractory
Bowen, 1986[40]	41		83	33										100% alloimmunized, refractory
Kickler, 1983[29]									27	100				100% alloimmunized, refractory
Kickler, 1985[36]										91				100% alloimmunized, refractory
Kickler, 1988[18]										94				100% alloimmunized, refractory
Brand, 1978[33]							100							100% alloimmunized, refractory
Ware, 1984[37]							84			90				100% alloimmunized, refractory
Gates, 1994[25]							89							100% alloimmunized, refractory
Filip, 1976[41]									72					100% alloimmunized, refractory
Heal, 1987[27]													67	100% alloimmunized, refractory
Freedman, 1984[32]										86				100% alloimmunized, most refractory
Sintnicolaas, 1996[24]	55						43					100		96% alloimmunized, refractory
Ogden, 1993[15]						96					96			84% alloimmunized, refractory
Rachel, 1988[19]		91						100						60% alloimmunized, most refractory
Kakaiya, 1984[10]	70		100	75										50% alloimmunized, most refractory
Yam, 1984[28]										87				<40% alloimmunized, refractory
McFarland, 1987[35]					93					100				Refractory (% alloimmunized NS)
Technique Mean	69	91	94	54	93	96	79	100	50	93	96	100	67	
Overall Mean			78						84				84	

* Data are reported as percentages.
† "With factors" indicates subgroup of patients, all of whom have nonimmune PLT-destructive factors.

excess of 70%. In the presence of some element of alloimmune PLT destruction, an incompatible cross-match would be expected to predict a poor outcome. Interestingly, low PPVs occurred exclusively in alloimmunized refractory patients, but were observed in only three studies (all three had provided HLA-selected products).[24,29,40]

DISCUSSION

The important question of whether cross-matched PLTs reduce hemorrhage or mortality has not been adequately addressed, as it has not for HLA-selected PLTs.[42] It has generally been assumed that improvements in PLT increments would also improve these outcomes, but this remains conjectural. The significant funding and resources needed to rigorously assess bleeding or identify small differences in already-low mortality rates generally preclude such studies. Only one study identified from this review even systematically gathered information on mortality, although statistical analysis was not possible.[30] Transfusion-refractory patients treated with PLTs cross-matched using the Capture-P assay had a higher rate of mortality than nonrefractory patients (45% vs. 33%). This has been observed in other studies as well, which have demonstrated that the refractory state is associated with increased mortality.[1] The specific role of cross-matching among transfusion-refractory patients, however, could not be assessed. No studies rigorously assessed bleeding in patients requiring cross-matched PLT support, although two did report hemorrhagic deaths among cross-matched PLT recipients.[20,30]

Cross-matching was originally developed to supplant the need for large panels of HLA-matched donors. This results in the provision of PLTs bearing HLAs less compatible with those of recipients. Concern has been expressed that this may result in the broadening of HLA alloimmunization and either development or worsening of alloimmune refractoriness. As observed in two studies we reviewed, neither the percentage of incompatible cross-matches nor the CCIs from compatible units appear to change appreciably throughout support.[20,22] The study by Petz and colleagues,[8] not specifically designed to examine the effect of cross-match support, did not observe much significant change in the breadth of alloimmunization, but did note that almost one-third of individuals receiving matched PLT support actually experienced a meaningful decrease in PRA. Other large studies have suggested that the breadth of alloimmunization tends to remain stable and, with longer periods of observation, actually declines in the majority of patients even with ongoing antigenic challenge with allogeneic cellular blood products.[43] None of the studies in this review were designed to assess the development or persistence of alloimmune refractoriness.

Three broad categories of patients were enrolled in the studies we reviewed: those with alloimmune refractoriness (with or without other causes), those with a wider variety of causes of refractoriness, and randomly selected patients with thrombocytopenia (a variable number of whom had PLT antibodies). Unequivocally, for HT patients alloimmunized against HLA or HPA, the substitution of cross-matched PLTs for randomly chosen apheresis or whole blood–derived pools results in improvements in count increments and the percentage of patients achieving variously defined transfusion success targets. Utility of the cross-match is also evident from the significant improvement in counts obtained after compatible transfusions versus those demonstrated to have been cross-match incompatible in this patient population.[18,24,25,27,29,32,34] In three of six cohorts with randomly selected patients with thrombocytopenia demonstrating less than 40% alloimmunization, no increment improvements were seen for compatible units versus incompatible ones[21,39] and in two of three techniques employed in a third study.[23] In support of this contention, for two such cohorts,[21,38] sensitivity was 0% to 18%, demonstrating the lack of utility of the cross-match in individuals without alloimmunization or refractoriness, whose cross-matches generally show quite high rates of compatibility.

In alloimmunized refractory HT patients, the success rate of cross-match–compatible PLTs, the NPV, generally ranged from 50% to 90%. The width of this range likely results from different proportions of nonimmune factors present in each group and variable robustness of selected cross-matching techniques. In an effort to isolate the count increment utility of cross-matching in these generally quite ill patients, a number of studies excluded individuals with nonimmune causes of PLT transfusion refractoriness. However, as Doughty and colleagues[44] observed, multiple nonimmune factors are present in up to 88% of failed PLT transfusions. Therefore, absolute estimates of cross-matching effectiveness based on highly selected, rather than real-life patient populations, may be misleading. Heal and colleagues[27] previously reported that the NPV was generally higher in patient cohorts selected to lack these factors. Similarly, in our reviewed studies, mean NPVs for unselected refractory alloimmunized patient groups, those selected for absence of nonimmune factors adversely affecting increments, and the subset of patients all of whom had one or more of these factors were 70, 81, and 54%, respectively (Table 2). Also, of four studies reporting NPVs both for unselected cohorts and for those selected to lack these factors, all demonstrated a higher NPV within the selected group.[15,19,24,35]

To date, the only prospective study comparing cross-matched to HLA-selected PLT support was conducted by Moroff and coworkers,[7] who found that identical matches had significantly higher 1-hour CCI success rates than HLA-mismatched units or cross-match–compatible units. Both of the latter approaches showed similar success rates. HLA-matched units of any variety had significantly higher 24-hour CCI success rates than cross-match–compatible PLTs. Petz and colleagues[8] found cross-matching to result in equivalent PPRs to those of HLA-identical units and antigen-negative units, all of which were superior to randomly chosen units. This study, however, included refractory patients who had no alloantibody and were given HLA-identical units, a significant source of bias in this arm.

Cross-matching can only be successful if compatible units can be found. While this is mainly influenced by the breadth of patient alloimmunization, the higher a technique's PPV, the lower the number of potentially compatible units erroneously identified as incompatible. In general, PPVs clustered around 80% in these cohorts. No technique-related pattern of false-positive failure was evident. Four studies reported the actual number of compatible units among the total cross-matched.[15,16,18,19] The percentage of cross-match–compatible units varied from 17% to 33% in transfusion-refractory cohorts with 60% to 100% alloimmunized recipients. Two other studies reported the mean number of compatible units as 41 and 60%.[20,22] Together, these suggest that a small number of broadly alloimmunized recipients can dramatically affect the overall number of cross-matches performed. Several studies reported that no compatible units could be found for some patients, excluding these individuals from cross-match support.[7,16,20,22]

With regard to cross-match techniques, among all studies using the PSIFT, reported NPVs were generally commensurate with or better than the means reported within the various subgroups of enrolled patients. Similar results were seen among the seven studies reporting NPVs for PRAT assays. There were too few reported NPVs to evaluate ELISA testing. LCT NPVs appeared equal to or below average patient population-expected values, with the majority of SPRCA NPVs below expected means.

In summary, cross-matching appears to be inferior to HLA identically matched units, but since these often cannot be found, cross-matching represents an alternative for patients who are not broadly alloimmunized against most other HLAs or against high-frequency HPAs. Cross-matching affords significantly improved PLT recovery and survival in refractory HT patients without severe intercurrent illness who have some element of immune PLT destruction, but it is unknown what impact such support will have on hemorrhage and mortality. There is no evidence to suggest that the imperfect matches that result from cross-matched units lead to broadening of alloimmunization or increase the difficulty of finding compatible units throughout a course of support. No one technique is ideal, but PLT cross-matching assays based on detection of bound recipient immunoglobulin appear superior to lymphocyte cross-matching or older

techniques. Compatibility identified with more than one technique may better predict successful PLT increments, but is generally impractical.

ACKNOWLEDGMENTS

The authors thank Ms Dolly Cordi and Ms Sue Ethier for locating the references.

CONFLICTS OF INTEREST

There are no conflicts of interest. NS is a consultant for Canadian Blood Services. Canadian Blood Services as a funding agency did not have any role in the design, analysis, and interpretation of the data or the preparation, review, and approval of the manuscript.

REFERENCES

1. Kerkhoffs JL, Eikenboom JC, van de Watering LM, van-Wordragen-Vlaswinkel RJ, Wijermans PW, Brand A. The clinical impact of platelet refractoriness: correlation with bleeding and survival. Transfusion 2008;48:1959-65.
2. Slichter SJ, Davis K, Enright H, Braine H, Gernshimer T, Kao KJ, Kickler T, Lee E, McFarland J, McCullough J, Rodey G, Schiffer CA, Woodson R. Factors affecting posttransfusion platelet increments, platelet refractoriness, and platelet transfusion intervals in thrombocytopenic patients. Blood 2005;105:4106-14.
3. Seftel MD, Growe GH, Petraszko T, Benny WB, Le A, Lee CY, Spinelli JJ, Sutherland HJ, Tsang P, Hogge D. Universal prestorage leukoreduction in Canada decreases platelet alloimmunization and refractoriness. Blood 2004;103: 333-9.
4. The Trial to Reduce Alloimmunization to Platelets Study Group. Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusions. N Engl J Med 1997;337:1861-9.
5. Vassallo RR Jr. New paradigms in the management of alloimmune refractoriness to platelet transfusions. Curr Opin Hematol 2007;14:655-63.
6. Slichter SJ. Platelet crossmatch testing for donor selection. Prog Clin Biol Res 1982;88:153-64.
7. Moroff G, Garratty G, Heal JM, MacPherson BR, Stroncek D, Huang ST, Ho W, Petz LD, Leach MF, Lennon SS, Rowe JT, Saleh MN, Arndt P, Foley K, Masel D, Postoway N. Selection of platelets for refractory patients by HLA matching and prospective crossmatching. Transfusion 1992;32: 633-40.
8. Petz LD, Garratty G, Calhoun C, Clark BD, Terasaki PI, Gresens C, Gornbein JA, Landaw EM, Smith R, Cecka JM. Selecting donors of platelets for refractory patients on the basis of HLA antibody specificity. Transfusion 2000;40: 1446-56.
9. Pai SC, Lo SC, Tsai SJ, Chang JS, Lin DT, Lin KS, Lin I. Epitope-based matching for HLA-alloimmunized platelet refractoriness in patients with hematologic diseases. Transfusion 2010;50:2318-27.
10. Kakaiya RM, Gudino MD, Miller WV, Sherman LA, Katz AJ, Wakem CJ, Krugman DJ, Klatsky AU, Kiraly TR. Four crossmatch methods to select platelet donors. Transfusion 1984;24:35-41.
11. Daly PA, Schiffer CA, Aisner J, Wiernik PH. Platelet transfusion therapy. One-hour posttransfusion increments are valuable in predicting the need for HLA-matched preparations. JAMA 1980;243:435-8.
12. Fowkes FG, Fulton PM. Critical appraisal of published research: introductory guidelines. BMJ 1991;302:1136-40.
13. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Moher D, Rennie D, de Vet HC, Lijmer JG. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. Ann Intern Med 2003;138:W1-12.
14. Sayed D, Bakry R, El-Sharkawy N, Zahran A, Khalaf MR. Flow cytometric platelet cross-matching to predict platelet transfusion in acute leukemia. J Clin Apher 2011;26:23-8.
15. Ogden DM, Asfour A, Koller C, Lichtiger B. Platelet crossmatches of single-donor platelet concentrates using a latex agglutination assay. Transfusion 1993;33:644-50.
16. O'Connell BA, Schiffer CA. Donor selection for alloimmunized patients by platelet crossmatching of random-donor platelet concentrates. Transfusion 1990;30: 314-17.
17. Freedman J, Gafni A, Garvey MB, Blanchette V. A cost-effectiveness evaluation of platelet crossmatching and HLA matching in the management of alloimmunized thrombocytopenic patients. Transfusion 1989;29:201-7.
18. Kickler TS, Ness PM, Braine HG. Platelet crossmatching. A direct approach to the selection of platelet transfusions for the alloimmunized thrombocytopenic patient. Am J Clin Pathol 1988;90:69-72.
19. Rachel JM, Summers TC, Sinor LT, Plapp FV. Use of a solid phase red blood cell adherence method for pretransfusion platelet compatibility testing. Am J Clin Pathol 1988;90: 63-8.
20. Wiita AP, Nambiar A. Longitudinal management with crossmatch-compatible platelets for refractory patients: alloimmunization, response to transfusion, and clinical outcomes. Transfusion 2012;52:2146-54.
21. Levin MD, van der Holt B, de Veld JC, Gratama JW, de Vries W, van't Veer MB. The value of crossmatch tests and panel tests as a screening tool to predict the outcome of platelet transfusion in a non-selected haematological population of patients. Vox Sang 2004;87:291-8.
22. Gelb AB, Leavitt AD. Crossmatch-compatible platelets improve corrected count increments in patients who are refractory to randomly selected platelets. Transfusion 1997; 37:624-30.
23. Köhler M, Dittmann J, Legler TJ, Lynen R, Humpe A, Riggert J, Neumeyer H, Pies A, Panzer S, Mayr WR. Flow cytometric detection of platelet-reactive antibodies and application in platelet crossmatching. Transfusion 1996;36: 250-5.

24. Sintnicolaas K, Löwenberg B. A flow cytometric platelet immunofluorescence crossmatch for predicting successful HLA matched platelet transfusions. Br J Haematol 1996;92: 1005-10.
25. Gates K, MacPherson BR. Retrospective evaluation of flow cytometry as a platelet crossmatching procedure. Cytometry 1994;18:123-8.
26. Chow MP, Yung CH, Hu HY, Tzeng JL, Lin JS, Lin WM, Lin CK. HLA antibodies – the cause of platelet alloimmunization in Chinese. Am J Hematol 1992;39: 15-19.
27. Heal JM, Blumberg N, Masel D. An evaluation of crossmatching, HLA, and ABO matching for platelet transfusions to refractory patients. Blood 1987;70:23-30.
28. Yam P, Petz LD, Scott EP, Santos S. Platelet crossmatch tests using radiolabelled staphylococcal protein A or peroxidase anti-peroxidase in alloimmunized patients. Br J Haematol 1984;57:337-47.
29. Kickler TS, Braine HG, Ness PM, Koester A, Bias W. A radiolabeled antiglobulin test for crossmatching platelet transfusions. Blood 1983;61:238-42.
30. Rebulla P, Morelati F, Revelli N, Villa MA, Paccapelo C, Nocco A, Greppi N, Marconi M, Cortelezzi A, Fracchiolla N, Martinelli G, Deliliers GL. Outcomes of an automated procedure for the selection of effective platelets for patients refractory to random donors based on cross-matching locally available platelet products. Br J Haematol 2004;125: 83-9.
31. Freedman J, Garvey MB, Salomon de Friedberg Z, Hornstein A, Blanchette V. Random donor platelet crossmatching: comparison of four platelet antibody detection methods. Am J Hematol 1988;28:1-7.
32. Freedman J, Hooi C, Garvey MB. Prospective platelet crossmatching for selection of compatible random donors. Br J Haematol 1984;56:9-18.
33. Brand A, van Leeuwen A, Eernisse JG, van Rood JJ. Platelet transfusion therapy. Optimal donor selection with a combination of lymphocytotoxicity and platelet fluorescence tests. Blood 1978;51:781-8.
34. Chow MP, Yung CH, Hu HY, Tzeng JL, Lin WM, Lin CK. Platelet crossmatching with lymphocytotoxicity test: an effective method in alloimmunized Chinese patients. Transfusion 1991;31:595-9.
35. McFarland JG, Aster RH. Evaluation of four methods for platelet compatibility testing. Blood 1987;69:1425-30.
36. Kickler TS, Braine H, Ness PM. The predictive value of crossmatching platelet transfusion for alloimmunized patients. Transfusion 1985;25:385-9.
37. Ware R, Reisner EG, Rosse WF. The use of radiolabeled and fluorescein-labeled antiglobulins in assays to predict transfusion outcome. Blood 1984;63:1245-8.
38. Skogen B, Christiansen D, Husebekk A. Flow cytometric analysis in platelet crossmatching using a platelet suspension immunofluorescence test. Transfusion 1995;35:832-6.
39. Lane D, Shivji S, Turner AR. Solid phase platelet crossmatching versus complement dependent lymphocytotoxicity – clinical utility. Prog Clin Biol Res 1990;337:59-62.
40. Bowen TJ, Berman-Wong E, Dawson D, Herbut B, Smith L, Snider C, Hill L. Comparison of three cross-match techniques to select platelet donors. Curr Stud Hematol Blood Transfus 1986;52:47-57.
41. Filip DJ, Duquesnoy RJ, Aster RH. Predictive value of crossmatching for transfusion of platelet concentrates to alloimmunized patients. Am J Hematol 1976;1:471-9.
42. Pavenski K, Rebulla P, Duquesnoy R, Saw CL, Slichter S, Tanael S, Shehata N. Efficacy of HLA-matched platelet transfusions for patients with hypoproliferative thrombocytopenia: a systematic review. Transfusion 2013; 53:2230-42.
43. Slichter SJ, Bolgiano D, Kao KJ, Kickler TS, McFarland J, McCullough J, Woodson R. Persistence of lymphocytotoxic antibodies in patients in the trial to reduce alloimmunization to platelets: implications for using modified blood products. Transfus Med Rev 2011;25:102-10.
44. Doughty HA, Murphy MF, Metcalfe P, Rohatiner AZ, Lister TA, Waters AH. Relative importance of immune and nonimmune causes of platelet-refractoriness. Vox Sang 1994;66:200-5.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Characteristics of the studies.
Table S2. Quality of studies.
Table S3. Estimates of screening tests in diagnostic accuracy studies.
Appendix S1. Search strategy: Ovid MEDLINE(R) <1946 to November Week 3 2012>, Embase <1974 to 2012 December 18>
Collaborators. The International Collaboration for Guideline Development, Implementation and Evaluation for Transfusion Therapies (ICTMG).