Provincial Platelet Audit Report

(Audit Period- January 9-April 7, 2017)

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1.0 Executive Summary

1.1 Background

Platelet transfusions are prescribed for the treatment or prevention of hemorrhage in patients with deficiency in total numbers and/or function of platelets, whether as a direct or indirect result of disease or as a consequence of medical treatment such as chemotherapy, massive transfusion or use of platelet inhibitors.

The useful shelf life of platelets is short (7 days from collection) and optimal storage is at room temperature; these factors are peculiar to platelets and result in two corresponding consequences – a tendency to high wastage rates due to "outdating", and facilitation of bacterial contamination and consequent risk of septic reaction (in addition to the hazards of transfusion in general).

Platelet transfusion is not without cost; a "dose" of platelets representing a single transfusion in Ontario costs about $270 to produce, and the cost of the in-hospital preparation and administration to the patient is estimated at 3 times that amount for a total of $1,080 to deliver each platelet pool to a patient and to manage all adverse reactions. Total current annual cost to provide and transfuse platelets in Ontario is estimated at $60 million. (See Section 2.1 below)

Numerous audits of platelet transfusion practice world-wide, using clinical indication criteria considered appropriate at the time, have revealed highly variable rates of deviation in platelet transfusion practice from these criteria with non-conformance rates commonly estimated in excess of 30% (see Appendix A). The clinical indication criteria for this audit process were tested in advance and validated in a pilot study (Etchells et al., 2018).

1.2 Purposes of This Audit

This audit is intended to assess the current state of the clinical practice of platelet transfusion in Ontario in respect of:

- Determining the proportion of platelet transfusions deemed inappropriate against defined, validated criteria
- Identifying the patient and provider factors associated with inappropriate platelet transfusion
- Providing guidance in the way of remediation efforts that could lead to improvements in the clinical practice of platelet transfusion
- Setting targets for Ontario hospitals to achieve in future institutional audits of platelet transfusion practice
- Estimating the annual costs to the Province of Ontario of inappropriate platelet transfusions
- Estimating the burden of preventable adverse transfusion reactions resulting from inappropriate platelet transfusions.

1.3 State of Practice

Over several decades criteria for prescribing of platelet transfusion have been the subject of intense debate and continuous scrutiny. Multiple "practice guideline" documents have been published and updated over the years, and used as the basis for audits. Earlier documents were largely based on observational studies and "expert opinion" and thus were not well-supported scientifically.

More recently, well-designed clinical trials have provided sound (but still evolving) guidance for the use of platelet transfusion in relatively stable hypo-proliferative thrombocytopenia (e.g. patients on chemotherapy or post-stem-cell transplant) which has resulted in recommended practices in such situations. For the most part, in other clinical situations for which platelet transfusion may be considered, the evidence defining specific criteria is less compelling, still depending on rather less rigorous information.

For the purposes of this audit, the criteria used were derived from recent guideline recommendations published by the American Association of Blood Banks (Kaufman et al., 2015a) and the International Collaboration for Transfusion Medicine Guidelines (Nahirniak et al., 2015).

Ontario ranks towards the lower end of the scale internationally and as the third highest province in Canada for the for platelet transfusion rate. *Per capita* platelet consumption in Ontario has been stable over the last five years at just over 4 doses/1000 population.

1.4 Design of the Audit

Hospitals were invited to participate and 69 (46%) of 150 eligible hospitals took part including all Teaching and Pediatric hospitals, representing approximately 90% of the platelet transfusion activity in Ontario. Data were collected in each hospital according to size, until either the requisite number of "orders" was achieved, or, failing this, data had been collected for 3 months, defined as:

- Small community hospital up to 50 beds, 3 months of data to a maximum of 10 platelet orders
- Medium-large community hospitals 50 or more beds, 3 months data to a maximum of 25 platelet orders
- Teaching (University-affiliated) medical centres, 3 months data to a maximum of 50 platelet orders

The audit was conducted between January 9th and April 7th, 2017.

Data were collected using a web-based audit tool and included: Hospital Site, Patient Care Area, Date of Transfusion, Patient Age and Sex, Number of Platelet Doses Ordered and Transfused, Ordering Physician Specialty, Indication for Transfusion, administration of antiplatelet therapies, patient bleeding status ["minor" (WHO grade 1 and 2) or "major" (WHO grade 3 and 4) (Miller et al., 1981)] and Pre- and Post-Transfusion Platelet Counts. Data for patients aged over 18 years ("Adults") and 18 years and under ("Pediatric") were analysed separately.

Hospitals were asked to report on whether or not they had measures in place to ensure appropriateness of the orders for platelet transfusion. Potential measures for which information was requested were:

- Use of Clinical Practice Guidelines
- Use of Pre-printed Orders Sets
- Use of Computerized Physician Order Entry (CPOE)
- Use of Prospective Order Screening
- Use of Audit and Feedback Mechanism

The criteria used in adjudicating the appropriateness of each platelet transfusion order are specified in detail in the body of the report. These criteria were developed based on recent published guidelines *(see above, 1.3)* by a panel of Transfusion Medicine specialists and validated in a pilot study. These criteria were applied to the data collected for "Adults" for this audit, using a computer-based algorithm which provided an adjudication for 88% of the reported platelet transfusion orders; 10% of these electronically adjudicated decisions were validated independently by two transfusion medicine specialists and showed 95% concordance. The remaining 12% of "Adult" adjudications, not successfully determined using the computer algorithm, were similarly adjudicated independently by two transfusion medicine specialists, and any differences in interpretation were resolved by consensus.
Data for "Pediatrics" were adjudicated separately by two Pediatric Transfusion Medicine specialists and differences similarly resolved by consensus. This provincial audit was unique in using established *a priori* appropriateness criteria concurrent with institutional guidelines validated in a pilot study (Etchells et al., 2018).

Principal Findings

- Sixty-nine of 150 eligible hospitals participated, comprising about 90% of platelet use in Ontario. Thus, this audit may be regarded as representative of the current platelet transfusion practices in the Province. A total of 1903 platelet transfusion orders were included, 1693 for Adult patients (age >18 yrs.) and 210 for pediatric patients (defined as age ≤18yrs).
- The adjudication criteria, compiled from recent recommendations by the American Association of Blood Banks (Kaufman et al., 2015a) and the International Collaboration for Transfusion Medicine Guidelines (Nahirniak et al., 2015), were independently evaluated and validated prior to the formal audit (Etchells et al., 2018).
- In Adults, the five specialties of physicians responsible for the majority of platelet transfusion orders were "Hematology/Oncology", "Critical/Intensive Care", "Hematology", "Surgery "and "Internal Medicine".
- The physician specialty with the lowest rate of inappropriate orders for platelet transfusion was "Hematology/Oncology" (28.6%) and the highest rate, "Anaesthesia" (75%). Between these two extremes, there was no significant statistical difference in the rates of inappropriate prescribing.

- About 60% of platelet transfusion orders were "prophylactic" for non-bleeding patients and 40% were either for patients with clinically apparent bleeding or in association with an invasive procedure or surgery.
- In Adult patients, platelet transfusion orders for Outpatients (mostly "Oncology/Hematology") had the lowest frequency of inappropriate orders; by contrast, the highest frequency of inappropriate orders was seen in acute care settings – intensive care units, emergency departments, operating rooms and acute care beds/units.
- The rate of inappropriate platelet orders was similar in Teaching (42.2%) and Community hospitals (40.3%).
- There was no significant difference in the overall rates of inappropriate platelet transfusion orders for non-bleeding patients, patients with clinically apparent bleeding and patients treated in connection with an invasive procedure.
- The pre-transfusion platelet count was reported in all but 16 cases. The lower the platelet count the higher the rate of appropriate platelet transfusion orders.
- The presence or absence of certain practices intended to enhance the appropriateness of platelet transfusion showed variability in success rates. The use of pre-printed order sets had a statistically significant effect on the rate of appropriateness for all hospitals while the use of Computerized Physician Order Entry and Prospective order screening as currently applied had a greater impact on appropriateness at Community hospitals than Teaching hospitals.
- Orders for platelet transfusion in children (≤18yrs.) were assessed in 210 episodes, the great majority in teaching hospitals. Most (85%) were for prophylaxis in non-bleeding patients. Inappropriate transfusion orders constituted almost two-thirds of the total in teaching hospitals and about half in community hospitals. The rates of inappropriate pediatric platelet transfusion orders were similar for all clinical settings examined, but for some categories the numbers of cases are small. At all platelet count levels above $10x10^9$/L, high rates of inappropriate orders were seen.
- Of 56 hospitals reporting on availability of hospital guidelines for platelet transfusion, 9 of 16 teaching hospitals and 22 of 40 community hospitals stated they had established such guidelines. The remaining 25 hospitals indicated they did not have such guidelines in place. The presence of documented, Transfusion Committee approved guidelines is a necessary pre-condition for monitoring clinical practice.
- Potential adverse transfusion events which could be attributable to inappropriate platelet transfusion at the rate measured in this audit has been assessed. Based on the following assumptions/information:
  - -Doses of platelets issued in Ontario annually (30% apheresis, 70% buffy coat pools of 4 doses) is approximately 60,000
  - -"Wastage" rate, principally due to outdating provincially is 12%,
  - -Inappropriate transfusion rate (based on this audit) is approximately 40%,
  - -The adverse reaction rates provided in Callum et al., 2016,
  - -It is estimated that, had these inappropriate transfusions **NOT** been given, 2 cases of symptomatic sepsis, 1-2 cases of anaphylaxis 220 cases of febrile non-hemolytic transfusion reactions and 600 cases of minor allergic reactions would have been avoided.
- In this audit, orders for multiple doses of platelets for transfusion occurred in 13% (239/1903) of platelet orders. In the UK study, multiple-dosing for prophylactic indications accounted for the following: 57 double-doses, 9 triple doses and 3 quadruple doses totally 153 doses in all (8% of total). Seventy-two (47%) of these multiple doses were given to patients with hematological diseases. (Charlton et al.,2014)
- Twenty-nine platelet orders were for management of idiopathic thrombocytopenic purpura (ITP). Of these only 3 with major bleeding were deemed appropriate. In 20 cases the indication was "prophylactic" in the absence of bleeding and in 6 cases the indication was "currently bleeding (minor bleed)". Thus, 26 of 29 (90%) of platelet transfusions for ITP were deemed inappropriate. The use of platelet transfusion in ITP should therefore be a particular focus for practice improvement. (Neunert et al.,2011)

1.5 Recommendations

1. Clinical Practice Recommendations

- Clinical Practice Recommendations for Adult platelet transfusion practice based on published clinical trial data and on recommendations of expert sources (American Association of Blood Banks, Kaufman et al., 2015a); International Collaborative for Transfusion Medicine Guidelines, Nahirniak et al., 2015) should be prepared and endorsed by an Ontario-based Expert Panel of Transfusion Medicine specialists. These recommendations should be distributed to all Ontario hospital Medical Directors of Transfusion Medicine and Chairpersons of hospital Transfusion Committees, with a view to endorsement by hospital Medical Advisory Committees (or equivalent) and incorporation into local hospital transfusion guidelines.
- Clinical Practice Recommendations for pediatric and neonatal platelet transfusion practice based wherever possible on published clinical trial data and recommendations of expert sources should be prepared and endorsed by an Expert Panel drawn from Ontario-based pediatric and neonatal Transfusion Medicine specialists and distributed to the Medical Directors of Transfusion Medicine and Chairs of hospital Transfusion Medicine Committees of all hospitals with pediatric medical services, with a view to endorsement by hospital Medical Advisory Committees (or equivalent) and incorporation into local hospital transfusion guidelines.
- Specialty organizations for physicians who are likely to prescribe platelet transfusion (e.g. anesthesiology, emergency medicine, intensive care, medical imaging, and surgery) should be approached with a view to obtaining formal endorsement of the Ontario Clinical Practice Recommendations, so established.

Defining reasons for current deviations from recommended practice

- Focus groups should be convened to examine the reasons for non-compliance with established guidelines, involving both physicians and nurses. A variety of possible explanations could include unawareness of guidelines, lack of confidence in guidelines due to perceived lack of clinical trial evidence, entrenched practice habits, patient demands, and fear of potential medico-legal consequences of restrictive transfusion practices.
- The output from these focus groups should inform the educational approach to promoting appropriate clinical practice and highlighting areas in need of additional studies.

2. Education for improvement

- For long-term effect, the optimal subject groups are medical students and residents in training. Appropriate educational content in undergraduate programs is required. Vigorous promotion of practice guidelines in Residency Training Programs can be made through the current “Boot Camp” transfusion medicine educational approach coordinated by the University of Toronto and distributed to all Ontario Medical schools, with assessment of knowledge outcomes (Lin et al., 2015). Recently, the self-directed online training program (Bloody Easy Lite for Physicians (http://belite.transfusionontario.org/) has been shown to be an effective, low-cost tool for enhancing physician transfusion knowledge (Lee et al., 2019). Inclusion of transfusion medicine content in Specialty Training Programs and in Royal College Fellowship candidate evaluation could provide additional incentive to improve practice related to the appropriate use of blood components and products (including platelets).
- For established practitioners, access to Continuing Medicine Education programs for transfusion medicine can provide an opportunity for improvement. Active consultation prior to designing the optimal knowledge translation strategy is suggested. In particular, the high volume prescribing practitioners in Hematology/Oncology, although having on the whole a lower incidence of platelet transfusions deemed “inappropriate” than others, nevertheless represent potentially the highest absolute number of unnecessary platelet transfusions and thus merit particular attention.
- Use of pre-printed order sets, computerized physician order entry and prospective order screening of platelet orders *(see 4. (i) below)* can provide further opportunities for educational intervention.

- The current population of "Transfusion Safety Officers" and Transfusion Nursing Practitioners combined with regular competency assessments offers a potential mechanism for informing those nurses who are actively involved in transfusion practice with the necessary guideline information (with particular support for nurses providing care for hematology/oncology patients).

3. Practice improvement

- An effective system is required for pre-transfusion screening of requests/orders for platelets for transfusion, matched to the Provincial Clinical Practice Recommendations (1, above). This audit establishes that pre-transfusion screening of platelet orders as currently applied shows only a limited beneficial effect in reducing inappropriate orders for platelet transfusion. Pre-transfusion order screening by technologists can be effective, but the effectiveness may be limited by reluctance to question orders due to workload concerns, anticipation of conflict with the ordering physician, or insufficient Transfusion Service Medical Director support.
- An effective computerized physician order entry (CPOE) system is required which matches the clinical and laboratory information about the patient to the Clinical Practice Recommendations, and indicates non-compliance. Non-compliance should include an information-supported physician "over-ride" which would require the ordering physician to consider the need for the transfusion, and if the decision to proceed is made to provide the rationale for the order.
- Deviations from guidelines recorded through the CPOE system would provide data for quarterly review of non-compliant orders at hospital Transfusion Committee meetings and offer the opportunity for an educational review in specific cases.
- Such recorded deviations identified through a CPOE system could also lead to Transfusion Committee audit, which could be incorporated into the hospital Quality Improvement Program.
- The application of pre-printed order sets in appropriate clinical circumstances offer the opportunity to enhance platelet transfusion ordering practices.
- Implementation of measures for practice improvement requires active support from the Medical Director of Transfusion Medicine, the Medical Advisory Committee (or equivalent) and Hospital Management.

4. Pediatric practice

- The high rate of inappropriate platelet transfusion orders in pediatric patients revealed by this audit indicates a need for particular attention. The fact that the majority of these orders are placed in a limited number of hospital settings suggests that the number of individuals needed to be involved in knowledge transmission initiatives is relatively small, and perhaps more susceptible to a more limited, targeted approach.

5. Consider devolution of costs of procuring blood components and products to hospitals

- Currently the costs of Canadian Blood Services for procuring and distributing blood components and products are met directly by the Provinces and Territories (except Quebec) by direct funding in proportion to the issue of red cell doses to each of those Provinces and Territories. Hospitals meet the costs of transfusion practice for storage, preparation of components and products and their administration but these costs are largely "buried" in the budgets for laboratories, nursing and supplies and are usually not specifically identified. Thus, there is no identifiable transfusion-specific cost to be considered in budgeting, and consequently in administrative scrutiny, which diminishes the attention paid to transfusion and its hospital oversight. Blood is perceived to be "free" at the point of consumption.
- If the procurement of blood components and products by hospitals were an identifiable and material cost to the hospital, there would be an incentive to pay more attention to their use including the appropriateness of prescribing practices. The current lack of motivation to limit inappropriate transfusion is a significant impediment to efforts to improve clinical transfusion practices. Oversight by hospital Transfusion Committees

would be encouraged and more exacting pre-transfusion screening would be supported if there were an identifiable cost associated with inappropriate transfusion.

- It is therefore recommended that the current funding model for provision of blood components and products be reviewed and the desirability of devolving costs to hospitals be assessed.

2.0 Background, Purpose and Evolution and Current State of Practice in Platelet Transfusion

2.1 Background

Platelet transfusions are prescribed for the prevention and treatment of hemorrhage in patients with deficiency in the number and/or function of platelets, either from primary clinical causes (e.g. acute leukemia causing hypoproliferative thrombocytopenia, liver disease with sequestration) or as an iatrogenic consequence of therapeutic measures (e.g. cytotoxic chemotherapy, dilution in massive transfusion, pharmaceutical inhibitors of platelet function). The clinical indications for which platelet transfusions are considered appropriate are more heterogeneous than those for red cells, and present the prescribers of platelet transfusion with more complex clinical decision-making questions and designers of audits with corresponding challenges in defining audit criteria for appropriateness. In addition, clinicians, nurses and patients are fearful of serious bleeding in thrombocytopenic patients, particularly intracranial bleeding, leading to defensive ordering. This practice is likely reinforced by lack of awareness by the clinical team of the serious hazard of septic transfusion reactions from platelets and therefore unable to appropriately weigh this in their risk-benefit decision-making.

Platelet transfusions present logistical challenges as a consequence of the short 7-day shelf-life of platelets which results in high wastage rates. Platelets for transfusion come in two forms, apheresis platelets prepared from single donors and "buffy coat" platelets pooled from whole blood donations from four separate donors resuspended in the plasma from one of the donors, specifically a male donor. These components are expensive, with supply costs estimated at $185 for one pool of buffy coat-derived platelets and $484 for a dose of apheresis platelets (Callum et al., 2016). Based on a proportion of 30% apheresis doses and 70% buffy coat pools supplied, the annual cost of procuring the almost 60,000 platelet doses used in Ontario in a year exceeds $16 million. While detailed estimates of the additional costs of processing and administration of platelet products in hospital have not been published, the additional costs of transfusion over and above those of procurement have been estimated at about 3-5 times the procurement costs alone for red cells and 10 times for frozen plasma (Shander et al., 2010, 2016). Thus, the overall cost of platelet transfusion in Ontario likely exceeds $60 million.

Platelets for transfusion, as with any blood component or derived product, have their own constellation of potential adverse consequences, including febrile non-hemolytic reactions, allergic reactions, hemolytic reactions from ABO-antibodies in the platelet-suspending plasma content of the component, Bacterial Contamination (BaCon), Transfusion-Related Acute Lung Injury (TRALI) and Transfusion-Associated Circulatory Overload (TACO). A particular predisposition to the consequences of BaCon is based on the requirement for storage at 20-24^{o} C; recent evidence suggests that traditional estimates of the risk of bacterial septic reactions (1:10,000 per platelet pool) may represent as little as one tenth of the true frequency (Benjamin, 2016; Hong et al., 2016).

Notes of caution are beginning to be sounded regarding the potential of platelet transfusions, in certain clinical circumstances, to be associated in more subtle ways with adverse outcomes. Examples include the PATCH study of platelet transfusion in the management of intracranial hemorrhage in patients on anti-platelet agents (APA) with normal platelet counts. This study showed higher rates of death and inferior neurological outcomes in patients receiving platelet transfusion (Baharoglu et al., 2016); platelet transfusion in patients with platelet counts above $100x10^9$/L and gastrointestinal bleeding while taking APA is associated with higher mortality without reduction in re-bleeding (Zakko et al., 2017). Curley et al. (2019) studying premature neonates with thrombocytopenia found increased major bleeding episodes and mortality when a higher transfusion threshold of $50x10^9$/L was used in comparison to a threshold of $25x10^9$/L.

Audits of platelet transfusion for clinical appropriateness have been carried out in many jurisdictions with widely varying outcomes, with up to two-thirds failing to fall within acceptable guideline criteria. Previous audits are listed in Appendix A

which also includes reference to the guidelines applied to each audit listed. The rates of inappropriate platelet transfusion in the various audits are to some extent determined by the rigor of the criteria used, which have tended to become more restrictive over time.

A large audit (more than 3,000 platelet transfusion episodes) in the UK (National Comparative Audit, April, 2011), using platelet transfusion indications similar to those in this Ontario audit, found that 62% of episodes met criteria for appropriateness, 28% were deemed inappropriate and 10% could not be adjudicated due to lack of clinical or laboratory information. Overall, 69% were for prophylactic treatment, 15% for active bleeding, and 13% pre-procedure (with a small number non-assignable due to missing information).

Major findings of this multicenter UK audit were:

- Platelet count within previous 24 hours – 92%
- Rationale for transfusion documented – 72%
- Transfusion deemed appropriate in 60% of prophylactic treatments, 64% of bleeding patients and 83% of pre-procedure orders.
- Of the procedures, 74% were classified as “minor”
- In only 30% was a post-transfusion platelet count obtained

A pilot audit was performed in preparation for this Province-wide audit in order to validate the proposed adjudication criteria (Etchells et al., 2018). Fifty platelet transfusion episodes at each of 4 academic medical centres were evaluated, 200 in total. This audit found an overall appropriate transfusion rate of 78%, 85% for prophylactic transfusion in non-bleeding patients and 73% in those receiving platelet transfusions for active bleeding. The lowest levels of appropriate use were associated with operating rooms (60%) and general surgery services (55%).

2.2 Purpose

This report describes the first Province-wide audit of the appropriateness of platelet transfusions in Ontario.

This audit is intended to:

- determine the proportion of inappropriate transfusions in Ontario hospitals
- identify the patient and provider factors associated with inappropriate use of platelet transfusion
- estimate the number of preventable adverse reactions to platelets if unnecessary transfusions were prevented
- estimate the annual cost to the healthcare system of unnecessary transfusions
- provide guidance in focusing remediation efforts to improve the appropriate use of platelets
- set indicators and targets for hospitals in Ontario to achieve on their audits of platelet transfusion practice

2.3 State of Practice

Recommendations for the decision to transfuse red cells address indications within a relatively narrow range of hemoglobin concentrations, taking into consideration the rate of any ongoing blood loss. Transfusion of frozen plasma is becoming less common with the availability of alternatives such as Prothrombin Complex Concentrates for reversal of warfarin effect, by a better understanding of the rebalanced coagulation disturbance in liver disease and the reduced therapeutic role of frozen plasma, and by realization that it has little or no value in the management of minor changes in laboratory indicators of coagulopathy (Callum et al, 2016; Canadian Society for Transfusion Medicine, 2019).

Platelets pose a more complex series of questions regarding their appropriate use, as a result of the interplay of platelet number and function, the presence or absence of anatomical lesions with enhanced risk of bleeding, procedural interventions, and the use of platelet function inhibitors and/or anticoagulants in thrombocytopenic patients. Much of the literature concerning indications for platelet transfusion focuses on the appropriate level of platelet count at which prophylactic platelet transfusion for hypoproliferative thrombocytopenia is appropriate, perhaps because that is the simplest clinical situation in which to perform clinical trials. Also, the recommendation of such a firm threshold may drive

prescribers to ensure clear maintenance of platelet counts above this level because of concern regarding clinical or medico-legal consequences.

Early conventional treatment of hypo-proliferative thrombocytopenia considered a threshold of less than $20x10^9$/L (NIH, 1987) as appropriate. Beutler (1993), in reviewing the historical and contemporary platelet transfusion practices, questioned the need for such a routine response and proposing a lower threshold in such cases. His suggestion was based in part on the classic observation of Slichter and Harker (1978) that the appearance of spontaneous gastro-intestinal blood loss in association with thrombocytopenia, in the absence of complicating pathological lesions, occurred when the platelet count fell to about $5x10^9$/L, and partly on the clinical observations of Gmur et al. (1991) indicating that thresholds lower than the traditional convention were no less safe. However, old habits die hard.

Several clinical trials following the Beutler (1993) review demonstrated that in uncomplicated hypo-proliferative thrombocytopenia in association with acute leukemia and its treatment, and following hemopoietic stem cell transplant, prophylactic platelet transfusion at thresholds of $10x10^9$/L and $20x10^9$/L had similar levels of bleeding complications (Rebulla et al., 1997; Heckman et al., 1997: Wandt et al., 1998; Zumberg et al., 2002; Estcourt et al., 2015a). Despite these results, significant proportions (up to 44%) of platelet transfusion events continue using thresholds above $10x10^9$/L (Greeno et al., 2007; Cameron et al., 2007). Application of a higher threshold platelet count for transfusion of platelets to patients with fever (>38 ^{o}C) was once common practice (British Committee for Standards in Haematology, 1992; Rebulla et al., 1997), but such escalation of the transfusion threshold is no longer routine (Nahirniak et al., 2015), and referred to merely as "may be advisable" in the presence of "high fever" (Schiffer et al. 2018). However, two studies emphasize that temperature elevations above 38^{o} C are associated with a significantly increased risk of bleeding in severe hypoproliferative thrombocytopenia (Webert et al., 2006; Stanworth et al., 2015). At the present time there are no clinical trial data to support a higher threshold than $10x10^9$/L in any subpopulation of patients, including in the pediatric population.

Current evidence supports the validity of platelet counts of $10x10^9$/L as a suitable threshold for prescribing prophylactic platelet transfusion in patients undergoing chemotherapy or bone marrow transplantation (Stanworth et al., 2013). Those receiving prophylactic platelet transfusion were significantly less liable to episodes of bleeding of WHO grade 2 or higher than those not receiving platelet transfusion, but the margin of difference was relatively small (Stanworth et al., 2013). "Choosing Wisely" Canada urges: "Don't routinely transfuse platelets for patients with chemotherapy-induced thrombocytopenia if the platelet count is greater than $10x10^9$/L in the absence of bleeding" (Canadian Society for Transfusion Medicine, 2019).

There is also debate over the appropriate dose of platelets for prophylaxis of bleeding. A trial (PLADO) of three dosage levels of 1.1, 2.2 and $4.4x10^{11}$ platelets per sq m of body surface area given at platelet counts of $10x10^9$/L or less showed no effect of dosage in frequency of bleeding; the lower doses resulted in more frequent platelet transfusion episodes but with reduction in the total number of doses transfused. However, patients receiving the highest dose experienced more transfusion-associated adverse events (Schlichter et al., 2010; Kaufman et al., 2015b; Zhao et al., 2017). (In Canada, only $2.2x10^{11}$/L platelet doses supplied by Canadian Blood Services are available, precluding adoption of the lower dose strategy used in the PLADO trial except at centres with sterile docking technology to split doses). By contrast, there is little reliable information addressing platelet count thresholds in more complex clinical situations, and clinical guidelines in these situations do not have clear evidential support from objective randomized clinical trials (Estcourt et al, 2015b; 2018a; 2018b; Schiffer et al., 2018). These situations include the management of thrombocytopenia complicated by bleeding of various severities and causes including concomitant anticoagulation; prophylactic platelet transfusion in anticipation of minor procedures (e.g. insertion of a central venous line, lumbar puncture, liver biopsy); more major interventions (particularly neuro-surgical procedures); or massive transfusion. Thus, recommendations regarding platelet transfusion thresholds in these situations cannot be based on high quality clinical trial evidence and the criteria used for this audit are rather based on observational evidence.

The American Association of Blood Banks (AABB) has recently published clinical guidelines for platelet transfusion (Kaufman et al., 2015a) and the International Collaboration for Transfusion Medicine Guidelines (ICTMG) published recommendations for platelet transfusion for hypoproliferative thrombocytopenia (Nahirniak et al., 2015). Other recent or

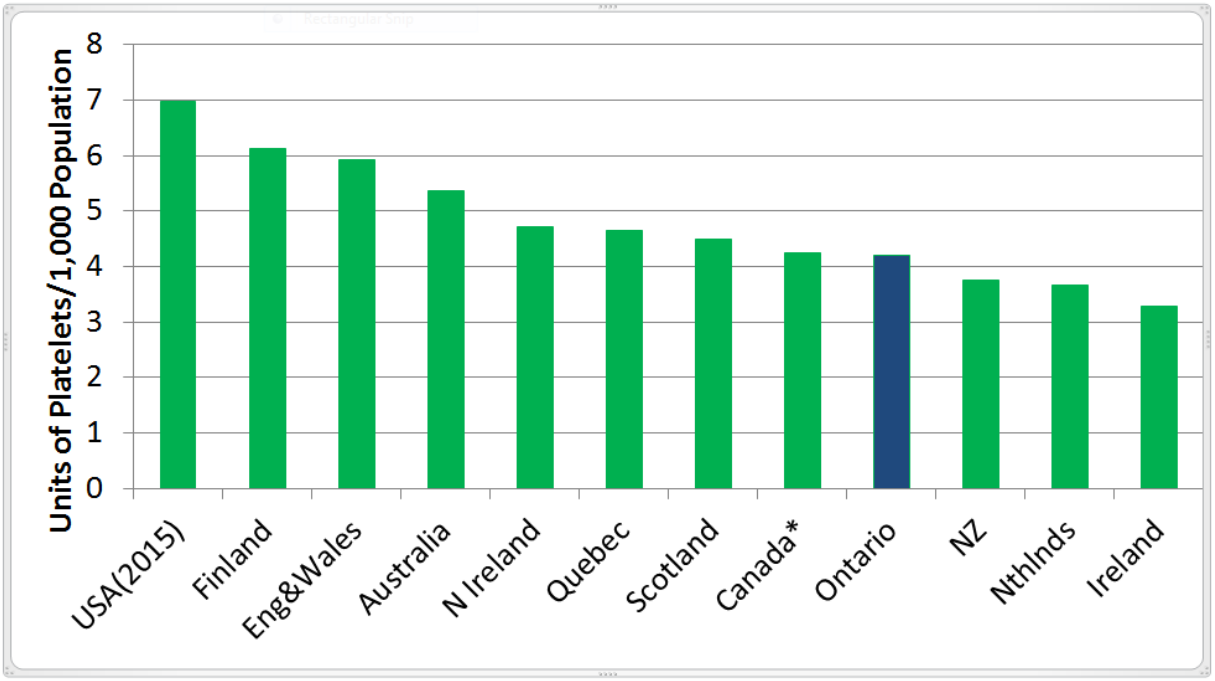
revised guidelines have been established by the British Society for Haematology (Estcourt et al., 2017), American Society of Clinical Oncology (Schiffer et al., 2018) and the Society of Interventional Radiology (Patel et al., 2019). These publications provide comprehensive and critical expert reviews of the available evidence leading to the formulation of the published guidelines, and detailed review of the data and information supporting these guidelines here would be superfluous.

The criteria for determination of appropriateness or inappropriateness for this audit of platelet use in Ontario are largely derived from the AABB and ICTMG Guidelines, modified to accommodate specific sets of clinical circumstances not addressed in the Guidelines. The detailed criteria for adjudication have been evaluated in the pilot study *(see above, 2.1)* in four academic medical centres in a retrospective chart review of 200 platelet transfusions (50 transfusions at each site), providing support for their relevance, applicability and reproducibility in assigning individual platelet transfusions to the appropriate or inappropriate categories (Etchells et al, 2018).

2.4 Platelet consumption in Ontario in perspective

Population based measures of platelet utilization in Ontario are compared here with practice internationally for countries for which comparable data are available (Figure 2.1) and the platelet utilization rate and the corresponding population base served over the 5 fiscal years are shown in Figure 2.2.

Figure 2.1 Platelet Doses (Apheresis and Pools) Issued per 1,000 Population for 2017 or Most Recent Year Available (*"Canada" represents Canadian data minus Ontario and Quebec).



These data are for comparable periods of time and are derived from the UK Serious Hazards of Transfusion Report (Bolton-Maggs et al., 2016), AABB data for the USA for 2014-15 (Rajbhandry et al., 2018) and the 2016 or 2017 on-line Annual Reports for the National Blood Transfusion Services for the other jurisdictions. Internationally, Canada's and Ontario's population-based platelet utilization is intermediate in relation to other countries.

Figure 2.2. Number of platelet doses issued (thousands) compared with the population (millions) for Ontario for 5 years 2012-13 to 2016-17

Figure 2.2 Illustrates the changes in the population of Ontario (in millions) and issues of platelet doses (in thousands) to Ontario hospitals by Canadian Blood Services over a 5 year period. The number of platelet doses issued in relation to population has remained relatively stable over this time.

3.0 Design and Methodology

3.1 Participating Hospitals and Data Collection

A prospective audit was undertaken of the clinical indications and laboratory data for a specified number of platelet transfusion episodes occurring in participating Ontario hospitals between January 9th and April 7th of 2017. A minimum number of platelet orders to be audited based upon hospital classification (to alleviate workload challenges) or specific time duration was required based upon the hospital classification; thus, data were collected until the specified number of orders had been reached, or, if less orders than specified were placed, data were collected for a 3 month period. Participation was voluntary.

Hospital Classification	**# of platelet orders/duration**
Small Community up to 50 beds	Minimum 10 platelet orders or 3 months of platelet orders
Medium to large Community >50 beds	Minimum 25 platelet orders or 3 months of platelet orders
Teaching	Minimum 50 platelet orders or 3 months of platelet orders

The data were collected using a web-based audit tool developed for this audit (created in collaboration with Inteloom Inc., Ottawa, Ontario). Access was restricted to each hospital by user ID and password. Data variables for collection chosen by the audit expert working group included:

- Hospital site
- Patient care area
- Date of transfusion
- Patient age (year of birth) and sex
- Concomittant use of antiplatelet and anticoagulant drugs
- Bleeding status
- Number of platelet doses ordered and transfused
- Ordering physician specialty
- Indication for platelet transfusion
- For pre-procedure, the type of procedure
- Pre- and post-transfusion platelet count results within 24 hours before or after transfusion respectively.

Sixty-nine (46%) of 150 eligible hospitals participated, representing approximately 90% of platelet use in Ontario during the study time period. Data on the 1903 platelet orders from 57 participating sites were received; 12 participating sites did not have any platelet orders during the audit period. Data on the indications for each transfusion order, including dose, were collected and the appropriateness of the clinical indication for each encounter was assessed according to criteria (see section 3.2 below) agreed in advance by a panel of transfusion medicine physicians. Each encounter was classified into one of 3 categories – "appropriate", "inappropriate" or "indeterminate" (where there was insufficient evidence and/or clinical and laboratory data to allow assignment). The data for Adult (age>18 years) platelet orders and pediatric/neonatal (age 18 years or less) platelet orders are reported separately.

3.2 Criteria for Adjudication as "Appropriate", "Inappropriate" or "Indeterminate"

The criteria for assessing the appropriateness of each platelet order were based primarily on the platelet transfusion guidelines recommended by the AABB (Kaufman et al., 2015a) and the ICTMG (Nahirniak et al., 2015), and were approved by a panel of six transfusion medicine physicians. The criteria are listed in Tables 3.1 and 3.2. For children (other than neonates), in the absence of clinical trial evidence or up-to-date consensus opinion, the same criteria as used for Adult patients were applied. Separate adjudication criteria were used for any neonatal platelet transfusions, using information from the literature (New et al., 2016) and agreed upon by consensus reached by the pediatric transfusion specialists participating in this audit process. (listed in Tables 3.3 and 3.4). Each order was adjudicated either electronically using Microsoft Excel formulas (Excel 16.28; Microsoft Corp.; Albuquerque, NM, USA) or, if the electronic adjudication did not conform to the electronically determined formula, independently adjudicated by two transfusion medicine physicians. All neonatal/pediatric platelet orders were adjudicated manually by two pediatric specialists. For any discrepancies between physician ratings as appropriate, inappropriate or indeterminate, the final rating was reached by consensus.

3.3 Adjudication Criteria

Table 3.1 Appropriate Adult Platelet Orders

For detailed list of references on which these criteria are based, see Etchells et al., 2018.

Clinical Setting	Platelet Count ($x10^9$/L)	Dose	Category
Prophylaxis for spontaneous bleeding Non-immune thrombocytopenia:			
• Thrombocytopenia due to hematologic malignancies, hematopoietic cell transplant, cytotoxic chemotherapy, sepsis or medication induced	≤ 10 ≤ 20 (outpt)	1 platelet pool	A1
• Acute promyelocytic leukemia (APL) – up to one week post induction or until coagulopathy resolves	<50	1 platelet pool	A2
• ECMO	<100	1 platelet pool	A3
Prophylaxis for surgery			
Invasive procedures:			
• Central venous catheter placement	<20	1 platelet pool	A4
• Vaginal delivery	<50	1 platelet pool	A5
• Lumbar puncture	<50	1 platelet pool	A6
• Liver biopsy, diagnostic endoscopy, transbronchial biopsy, laparotomy, vascular invasive procedures, other major procedures	<50	1 platelet pool	A7
• Epidural anesthesia	<80	1 platelet pool	A8
Major non-neuraxial surgery or procedures	<50	1-2 platelet pools	A9
Neuro or ocular surgery (exception: cataract surgery) • Taking antiplatelet agents	<100 Any	1-2 platelet pools	A10
Therapeutic anticoagulation that cannot be stopped	<30	1 platelet pool	A17
Therapeutic			

Immune Thrombocytopenia, serious major bleeding	<50 (non-ICH) <100 (ICH)	1-2 platelet pools	A11
Non -Central Nervous System (CNS) minor bleeding, not in surgery	<30 <50 (outpt)	1 platelet pool	A12
Non - CNS major bleeding, not in surgery	<100	1 platelet pool	A13
Non-CNS bleeding major bleeding or neuro/ocular bleeding or up to 1 month after ICH, not in surgery	<100	1-2 platelet pools	A14
Major elective non-neuraxial surgery or procedures associated with major blood loss > 500 ml (up to 48 hours post-op)	<50	1 platelet pool	A15
Minor bleeding during surgery (non-cardiac, non-neuro)	<30	1 platelet pool	A15.5
Neuro or ocular surgery (exception: cataract surgery) (up to 48 hours post-op)	<100	1 platelet pool	A16
Actively bleeding (WHO grade > 2) patients with platelet dysfunction: • Acquired i.e. antiplatelet agents, myeloproliferative disorders, aplastic anemia • Cardiac surgery patients with perioperative bleeding and thrombocytopenia and/or suspected platelet abnormalities due to cardiopulmonary bypass circuit • Inherited (Wisott-Aldrich syndrome, Bernard Soulier syndrome, Glanzmann thrombosthenia)	Any	1 platelet pool	A18
Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), and heparin induced thrombocytopenia (HIT) (WHO grade 4 bleeding)	Any	1 platelet pool	A19

Table 3.2 Inappropriate Adult Platelet Orders

Clinical Setting	**Platelet Count ($x10^9$/L)**	**Dose**	**Category**
Prophylaxis for spontaneous bleeding Non-immune thrombocytopenia:			
• Thrombocytopenia due to hematologic malignancies, hematopoietic cell transplant, cytotoxic chemotherapy, sepsis or medication induced	>10 >20 (outpt)	1 platelet pool	I1
• Acute promyelocytic leukemia (APL) – up to one week post induction or until coagulopathy resolves	≥ 50	1 platelet pool	I2
• ECMO	≥100	1 platelet pool	I3
Prophylaxis for surgery *Invasive procedures:*			
• Central venous catheter placement	≥ 20	1 platelet pool	I4
• Vaginal delivery	≥ 50	1 platelet pool	I5
• Lumbar puncture	≥ 50	1 platelet pool	I6
• Liver biopsy, diagnostic endoscopy, transbronchial biopsy, laparotomy, vascular invasive procedures, other major procedures	≥ 50	1 platelet pool	I7
• Epidural anesthesia	≥80	1 platelet pool	I8
Major non-neuraxial surgery or procedures	≥ 50	1-2 platelet pools	I9
Neuro or ocular surgery (exception: cataract surgery) • Taking antiplatelet agents	≥ 100 Any	1-2 platelet pools	I10
Therapeutic anticoagulation that cannot be stopped	≥30	1 platelet pool	I17
Therapeutic			
Immune Thrombocytopenia (ITP), serious major bleeding	≥50 (non-ICH) ≥100 (ICH)	1-2 platelet pools	I11

Prophylactic transfusion for ITP	Any	Any	I11.5
Non - CNS minor bleeding , not in surgery	≥30 ≥50 (outpt)	1 platelet pool	I12
Non-CNS major bleeding, not in surgery	≥100	1 platelet pool	I13
Neuro/ocular bleeding or up to 1 month after ICH	≥100	1-2 platelet pools	I14
Major elective non-neuraxial surgery or procedures associated with major blood loss > 500 ml (up to 48 hours post-op)	≥50	1 platelet pool	I15
Minor bleeding during surgery (non-cardiac, non-neuro)	≥50	1 platelet pool	I15.5
Neuro or ocular surgery (exception: cataract surgery) (up to 48 hours post-op)	≥100	1 platelet pool	I16
Actively bleeding (WHO grade < 2-minor) patients with platelet dysfunction: • Acquired i.e. antiplatelet agents, myeloproliferative disorders, aplastic anemia • Cardiac surgery patients with perioperative bleeding and thrombocytopenia and/or suspected plt abnormalities due to cardiopulmonary bypass circuit • Inherited (Wisott-Aldrich syndrome, Bernard Soulier syndrome, Glanzmann thrombosthenia)	Any	1 platelet pool	I18
Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), and heparin induced thrombocytopenia (HIT) (WHO grade <4)	Any	1 platelet pool	I19

Table 3.3 Classifications of Appropriate Neonatal Platelet Orders*

Clinical Setting	Platelet Count ($x10^9$/L)	Category
Term Infants	< 20	nA1
Pre-term > 7 days old Neonatal Alloimmune Thrombocytopenia	< 30	nA2
Pre-term and ≤ 7 days old Pre non-neuraxial surgery Concurrent coagulopathy Previous significant hemorrhage (i.e. grade 3-4 intraventricular or pulmonary hemorrhage) Active Bleeding	< 50	nA3
Pre neuraxial surgery	< 100	nA4

Table 3.4 Classifications of Inappropriate Neonatal Platelet Orders*

Clinical Setting	Platelet Count ($x10^9$/L)	Category
Term Infants	≥ 20	nI1
Pre-term > 7 days old Neonatal Alloimmune Thrombocytopenia	≥ 30	nI2
Pre-term and ≤ 7 days old Pre non-neuraxial surgery Concurrent coagulopathy Previous significant hemorrhage (i.e. grade 3-4 intraventricular or pulmonary hemorrhage) Active Bleeding	≥ 50	nI3
Pre neuraxial surgery	≥100	nI4

*The setting of criteria and the conduct of this audit preceded the availability of the results of a large randomized trial of platelet transfusion thresholds in premature neonates (Curley et al., 2019; Estcourt, 2019) and thus do not meet the conditions that would be recommended as a consequence of that trial. Had those data been available it is likely that more stringent threshold criteria ($<25x10^9$ /L) would have been applied to this audit and hence the inappropriate classification more frequently assessed.

3.3 Reporting Results to Participating Hospitals

The details for each hospital's individual patient/transfusion data together with the interpretation as "Appropriate", "Inappropriate" or "Indeterminate" for each case will be provided in a site specific report. The report for each institution should be communicated to the Chief Executive Officer, the Chairperson of the Transfusion Committee, and the Medical Director and the Manager of the Transfusion Medicine Service.

4.0 Validation Procedures

4.1 Validation of Data Collection Process

Verification and validation procedures occurred during the data collection period and at the end of the final data entry period. As part of the verification process a data entry validation was performed between manual collection forms and the electronic data tool. Nine participating hospitals provided manual collection forms for validation allowing 192/1903 total orders, approximately 10% to be compared. There was a 99% (191/192) agreement rate between the manual entry sheets and the electronic audit tool with any discrepancies in data entry being resolved.
It was concluded the discrepancies in the database were assessed as sufficiently rare as to not materially affect the adjudication of orders, analysis and/or conclusions for the audit.

4.2 Validation of Adjudication Criteria

A pilot study applying these criteria (Tables 3.1/3.2) in a chart review of 50 platelet transfusion episodes in each of four academic medical centres established a high degree of concordance (95%) in independent physician assessment of appropriateness or inappropriateness of individual episodes, confirming practical applicability (Etchells et al., 2018). This study also provided evidence regarding differing rates of inappropriate platelet transfusion under a variety of clinical circumstances, suggesting an opportunity for revealing areas for improvement in clinical practice.

4.3 Validation of the Electronic Adjudication Process

Electronic adjudication was performed in Microsoft Excel (Excel 16.28; Microsoft Corp.; Albuquerque, NM, USA) using formulas. A total of 1493 orders were adjudicated using this "automated" formula based method. All the additional Adult platelet orders not evaluable by the electronic process were adjudicated by two hematologists independently. All pediatric/neonatal orders (patients ≤ 18 years of age) were also adjudicated independently by two pediatric hematologists. A sub-set of electronically adjudicated orders were manually adjudicated to validate the electronic adjudication method; the agreement percentage between electronic and manual adjudication was without affecting appropriate/inappropriate ratings was 91%, deemed insufficient to materially affect the audit conclusions.

5.0 Platelet Audit Results

The following two graphs present a concise overview and summary of the results of adjudication of the Adult patient platelet transfusion audit process. Figure 5.1 shows the distribution of the proportion of Adult platelet transfusion orders deemed "inappropriate" by each of the 57 hospitals reporting data, and indicates the median value and the interquartile range. Figure 5.2 presents a summary for each of the 57 reporting hospitals of the absolute numbers of both total platelet transfusion orders reported and the corresponding number deemed "inappropriate".

Figure 5.1

For each of the 57 participating hospitals, the percentage of orders for platelet transfusion to Adult patients which were deemed “inappropriate”, ranging from 0 – 100% with a median value of 46% and interquartile range of 30-51%. Each bar represents one reporting hospital and the percentage of platelet transfusions deemed “inappropriate” is shown for each reporting hospital.

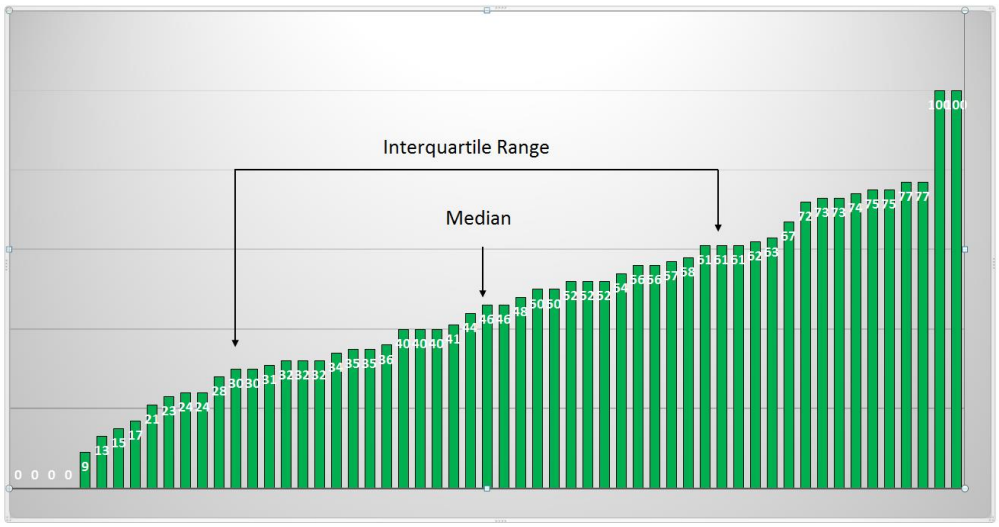
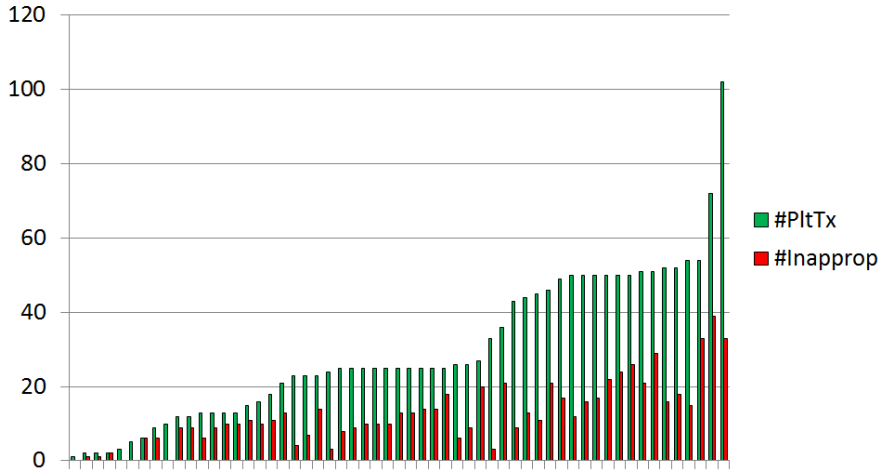


Figure 5.2

This chart illustrates, for each of the 57 participating hospitals, the total absolute numbers of orders for platelet transfusion to Adult patients (green bars) and the absolute numbers that were deemed “inappropriate” (red bars). Each pair of bars (green and red) represents the absolute number of platelet transfusions (green) and the absolute number deemed “inappropriate” (red) for each of the reporting hospitals.



5.1. Audit results for Adult Patients ≥ 18 yrs.

Table 5.1.1. Total Adult platelet orders/transfusions

	All Hospitals (n= 57 sites)	Community Hospitals (n=41 sites)	Teaching Hospitals (n=16 sites)
Total # platelet orders	1693	1033	660
# of doses of platelets ordered	1957	1200	757
Median # doses ordered (min-max)	1 (1-4)	1 (1-4)	1 (1 or 2)
# of doses of platelets transfused	1860	1163	697
Median # doses transfused (min-max)	1 (1-3)	1 (1-3)	1 (1 or 2)

Table 5.1.1. Shows the distribution of platelet orders/transfusions including median/minimum/maximum number of platelet doses ordered/transfused for all hospitals, community hospitals and teaching hospitals.

Dose of Platelets ordered/transfused for Adults

Figure 5.3.1. Distribution of platelet doses ordered/transfused as reported by audit participants (1 "dose" is equivalent to 1 pooled or 1 apheresis platelet dose).

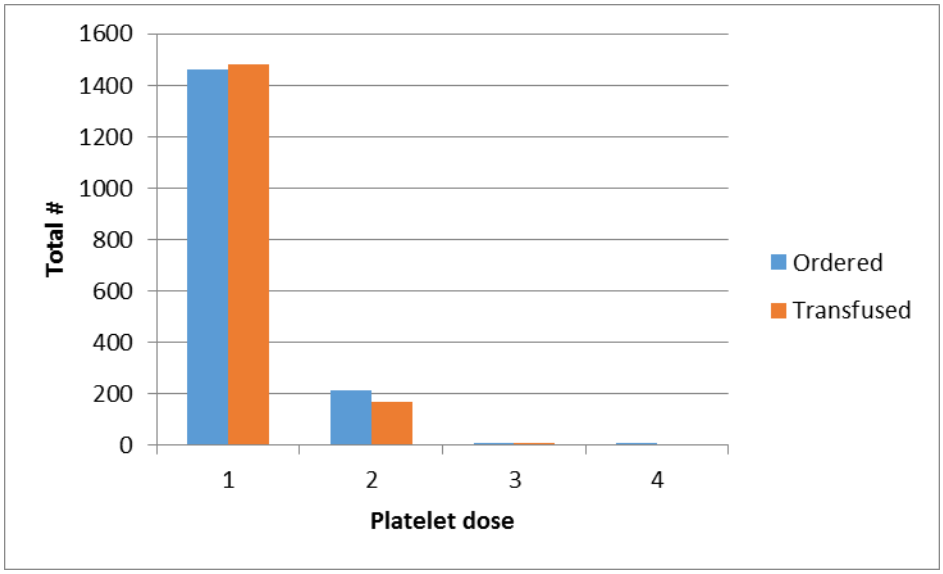


Figure 5.3.1. Frequency/distribution of platelet doses ordered/transfused. Total number of single platelet doses transfused is greater than total number of single platelet doses ordered as 10 original multiple dose platelet orders were reduced to single dose transfusions as a result of technologist prospective screening process or a Transfusion Medicine laboratory physician consult.

Table 5.1.2. Lists the specialties of the physicians ordering platelet transfusions for Adult patients >18 years of age.

Specialty ordering platelets	Total # (%)	Community # (%)	Teaching # (%)
Hematology/Oncology	662 **(39.1)**	405 (39.2)	257 (38.9)
Critical Care/Intensive Care	288 **(17.0)**	207 (20.0)	81 (12.3)
Surgery	212 **(12.5)**	65 (6.3)	147 (22.3)
Internal Medicine	200 **(11.8)**	126 (12.2)	74 (11.2)
Emergency	81 **(4.8)**	61 (5.9)	20 (3.0)
Hospitalist	67 **(3.9)**	51 (4.9)	16 (2.4)
Family Medicine	59 **(3.5)**	59 (5.7)	0 (0.0)
Anesthesia	56 **(3.3)**	32 (3.1)	24 (3.6)
Other	39 **(2.3)**	13 (1.3)	26 (4.0)
Obstetrics/Gynecology	20 **(1.2)**	12 (1.2)	8 (1.2)
Unknown	8 **(0.5)**	2 (0.2)	6 (0.9)
Radiology	1 **(0.1)**	0 (0.0)	1 (0.2)
Total	1693	1033	660

Table 5.1.2. Presents the data defining the clinical services from which orders for platelets originated. Hematology/Oncology represented 39.1% of the platelet orders with 17.0% from Critical Care/Intensive Care and 12.5% from Surgery for all hospital classifications. In Community hospitals, the top 2 platelet ordering specialties were Hematology/Oncology and Critical Care/Intensive Care representing 39.2% and 20.0% respectively. In Teaching hospitals the top 2 platelet ordering specialties were Hematology/Oncology and Surgery representing 38.9% and 22.3% respectively.

Table 5.1.3. Transfusions Deemed Appropriate vs Inappropriate (Excluding Indeterminate category) for All Hospitals by Medical Specialty of Ordering Physician (>20 platelet orders).

Indeterminate category were very few and would not invalidate the general conclusions; hence, the number of orders for platelets unaccounted for would be quite small.

Specialty	Total Orders	Appropriate # (%)	Inappropriate # (%)	*p value*
Anesthesia	56	14 (25.0)	42 **(75.0)**	<0.006
Internal Medicine	198	95 (48.0)	103**(52.0)**	NS
Critical care	284	139 (48.9)	145 **(51.1)**	NS
Emergency	80	40 (50.0)	40 **(50.0)**	NS
Hospitalist	67	34 (50.7)	33 **(49.3)**	NS
Surgery	205	109 (53.2)	96 **(46.8)**	NS
Obstetrics/Gynecology	20	11 (55.0)	9 **(45.0)**	NS
Family Medicine	59	37 (62.7)	22 **(37.3)**	NS
Hematology/Oncology	661	472 (71.4)	189 **(28.6)**	<0.05

Table 5.1.3. Presents the proportions of appropriate and inappropriate orders by medical specialty of order physician, ranked by ascending order of platelet transfusions deem inappropriate. Hematology/Oncology represents the lowest percentage of inappropriate platelet utilization (28.6%) while Anesthesia represented the "highest" percentage of inappropriate platelet utilization (75.0%). The "Indeterminate" category was omitted from this analysis.

Table 5.1.4. Clinical services to which the platelets were issued:

Platelet Issued Location	Total # (%)	Community # (%)	Teaching # (%)
Inpatient - Other	554 (32.7)	304 (29.4)	250 (37.9)
Inpatient ICU (include any ICU such as CCU, CVICU, Neuro ICU)	467 (27.6)	299 (28.9)	168 (25.4)
Outpatient clinic (Oncology, Hematology, Other)	332 (19.6)	275 (26.6)	57 (8.6)
Operating room (including Recovery Room)	167 (9.9)	56 (5.4)	111 (16.8)
Emergency	116 (6.9)	81 (7.8)	35 (5.3)
Other	53 (3.1)	17 (1.6)	36 (5.5)
Diagnostic imaging	4 (0.2)	1 (0.1)	3 (0.5)
Total	1693	1033	660

Table 5.1.4. Presents the location within the hospitals to which platelets were issued and where transfusion of platelets was assumed to have taken place. Inpatient-other and Inpatient-ICU categories were 32.7% and 27.6% respectively of all the platelet doses transfused (patient age>18). The next most frequent areas for platelet transfusion were the Outpatient clinic-Oncology (19.6%) and the operating room (9.9%).

Table 5.1.5. Clinical Indication for Platelet transfusion for Adult patients >18 yrs.

Transfusion Indication	Total # (%)	Community # (%)	Teaching # (%)
Prophylactic (non-bleeding, no procedure)	1032 (61.0)	689 (66.7)	343 (52.0)
Therapeutic (currently bleeding)	515 (30.4)	266 (25.7)	249 (37.7)
Prophylactic (before invasive procedure)	146 (8.6)	78 (7.6)	68 (10.3)
Total	1693	1033	660

Table 5.1.5. Presents the clinical indication for platelet transfusion orders. Prophylactic (non-bleeding, no procedure) represents 61.0% of platelet orders while therapeutic (currently bleeding) and Prophylactic (before invasive procedure) represent 30.4% and 8.6% respectively for All hospitals.

Table 5.1.6. Bleeding status for Platelet transfusions in Therapeutic (currently bleeding) category Adult patients

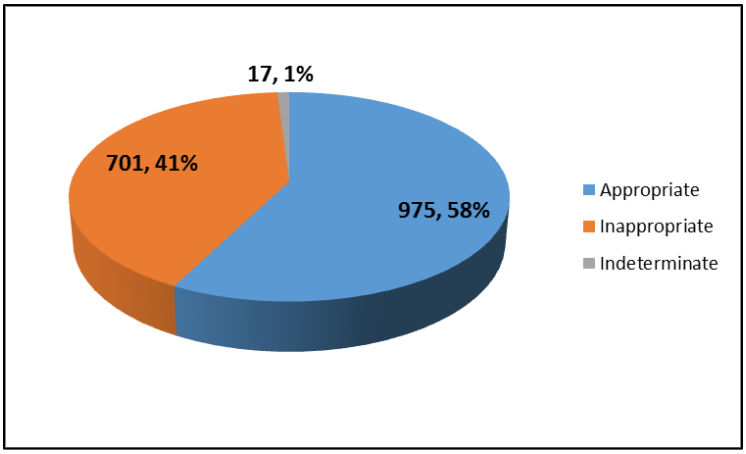
Bleeding status (currently bleeding)	Total # (%)	Community # (%)	Teaching # (%)
Major bleed (WHO Grade 3-4)*	295 (57.3)	151 (56.8)	144 (57.8)
Minor bleed (WHO Grade 1-2)*	220 (42.7)	115 (43.2)	105 (42.2)
Total	515	266	249

*(Miller et al., 1981)

Appropriateness of Platelet Orders

Figure 5.4. Overall classification of Adult platelet transfusion orders. Of the 1693 (excluding patients ≤18 years) orders for platelets, 975 (57.6%) were classified as appropriate while 701 (41.4%) were deemed inappropriate and 17 (1.0%) were indeterminate.

Figure 5.4. Adult orders (patients >18 years old) n=1693



Appropriateness of orders for Platelet transfusions by Hospital Classification

Table 5.1.7. The proportion of Adult platelet orders deemed "appropriate", "inappropriate" or "indeterminate" by hospital classification, number and percentage

Hospital classification	Appropriate #/ (%)	Inappropriate #/ (%)	Indeterminate #/ (%)	Total
Community	590 (57.1)	435 (42.1)	8 (0.8)	1033
Teaching	385 (58.3)	266 (40.3)	9 (1.4)	660
Total	975	701	17	1693

Table 5.1.8. Transfusion Deemed Appropriate vs. Inappropriate by Clinical category for All Hospitals

Clinical Category	Total # (%)	Appropriate # (%)	Inappropriate # (%)	*p value*
Pre-procedure (before invasive procedure)	139 (8.3)	89 (64.0)	50 (36.0)	NS*
Prophylactic (non-bleeding, no procedure)	1027 (61.3)	596 (58.0)	431 (42.0)	NS*
Therapeutic (currently bleeding)	510 (30.4)	290 (56.9)	220 (43.1)	NS*

Table 5.1.8. Each Clinical category compared by Simple 2x2 Chi Square Test with the overall totals. Rows categorized by lowest to highest % inappropriate. (Orders deemed "indeterminate" have been excluded from the calculations as the numbers are small and do not influence the conclusions)

Table 5.1.9. Platelet Transfusions Deemed Appropriate vs. Inappropriate by Clinical Indication for Community and Teaching Hospitals

Community Hospitals *(n=41 sites; 1025 platelet orders)*				
Clinical Indication	**Total #**	**Appropriate # (%)**	**Inappropriate # (%)**	***p value***
Therapeutic (currently bleeding)	264 (25.8)	155 (58.7)	109 **(41.3)**	NS*
Pre-procedure (before invasive procedure)	75 (7.3)	43 (57.3)	32 **(42.7)**	NS*
Prophylactic (non-bleeding, no procedure)	686 (66.9)	392 (57.1)	294 **(42.9)**	NS*
Total	**1025**	**590 (57.6)**	**435 (42.4)**	

Teaching Hospitals *(n=16 sites; 651 platelet orders)*				
Clinical Indication	**Total**	**Appropriate # (%)**	**Inappropriate # (%)**	***p value***
Pre-procedure (before invasive procedure)	64 (9.8)	46 (71.9)	18 **(28.1)**	<0.05
Prophylactic (non-bleeding, no procedure)	341 (52.4)	204 (59.8)	137 **(40.2)**	NS*
Therapeutic (currently bleeding)	246 (37.8)	135 (54.9)	111 **(45.1)**	NS*
Total	**651**	**385 (59.1)**	**266 (40.9)**	

**NS- Not statistically significant*

Table 5.1.9. Individual categories were compared to respective totals by Simple 2x2 Chi Square Test. There is no statistically significant difference between the overall proportion of appropriate and inappropriate transfusions when Community and Teaching Hospital data are compared except for "Pre-procedure- before invasive procedure" category where Teaching hospitals have a statistically significant lower percentage of inappropriate orders.

Table 5.1.10. Platelet Transfusions Deemed Appropriate vs. Inappropriate for All Hospitals by Issue Location

Issue Location	**Total # (%)**	**Appropriate # (%)**	**Inappropriate # (%)**	***p value***
Outpatients-(Oncology, Hematology, Other)	330 (19.7)	287 (86.7)	43 **(13.3)**	<0.001
Inpatients	554 (33.1)	323 (58.3)	231 **(41.7)**	NS*
Other	54 (3.2)	30 (55.6)	24 **(44.4)**	NS*
Emergency	114 (6.8)	55 (48.2)	59 **(51.8)**	<0.04
Operating Room	160 (9.5)	72 (45.0)	88 **(55.0)**	<0.002
Intensive Care	464 (27.7)	208 (44.8)	256 **(55.2)**	<0.002
Total	**1676**	**975**	**701**	

**NS- Not statistically significant. Note-Indeterminate orders (17) are not included in the table.*

Table 5.1.10. Outpatient platelet transfusions are significantly less likely to be inappropriate, possibly because there is likely a high proportion of transfusions prescribed in this situation by hematologists/oncologists who tend

to be more familiar with and confident in application of transfusion guidelines or is protocolized with a medical directive for the transfusion nurses. Higher inappropriate transfusion rates are seen in acute care settings where the temptation to pre-emptive transfusion decisions may be greater.

Table 5.1.11. Platelet Transfusions Deemed Appropriate vs. Inappropriate by Pre-transfusion Platelet Counts for All Hospitals

Pre-transfusion platelet counts	Appropriate # (%)	Inappropriate # (%)	Indeterminate # (%)
≤ 10*	572 (95.7)	26 (4.3)	0 (0.0)
11-25	197 (44.0)	251 (56.0)	0 (0.0)
26-50	104 (41.3)	147 (58.3)	1(0.4)
51-99	48 (27.1)	129 (72.9)	0 (0.0)
≥100	48 (25.8)	138 (74.2)	0 (0.0)
No platelet count reported	6 (18.7)	10 (31.3)	16 (50.0)
Total	975	701	17

Table 5.1.11. Presents the relationship between platelet count and appropriateness of the platelet transfusion. There is an inverse correlation between the proportion of appropriate transfusions in each category and the maximum platelet count defining that category. (R= -0.823)

- *In the ≤10 platelet count category analysis 29 platelet orders were for ITP indications. 3 ITP- major bleed deemed appropriate; 20 ITP- prophylactic, no bleeding deemed inappropriate; 6 ITP- currently bleeding (minor bleed) deemed inappropriate.
- All but 32 (<2%) of Adult platelet transfusion episodes reported that a pre-transfusion platelet count was recorded.

Table 5.1.12. **Summary of frequency of reasons transfusion orders for platelets were deemed "appropriate", "inappropriate" or "indeterminate"**

Code	# of orders (%)	Code Description
Appropriate (N=975)		
A1	584 (59.9)	**Prophylaxis for spontaneous bleeding** • Non-immune thrombocytopenia • Thrombocytopenia due to hematologic malignancies, hematopoietic cell transplant, cytotoxic chemotherapy, sepsis or medication induced • Platelet count ≤10; ≤20 (outpatient)
A12	102 (10.5)	**Therapeutic** • Non - CNS bleeding (WHO grade 2) • Platelet count <30; <50 (outpatient)
A13	92 (9.4)	**Therapeutic** • Non - CNS bleeding (WHO grade 3) • Platelet count <100
A18	77 (7.9)	**Therapeutic** Actively bleeding (WHO grade > 2) patients with platelet dysfunction: • Acquired i.e. antiplatelet agents, myeloproliferative disorders, aplastic anemia • Cardiac surgery patients (n=75) with perioperative bleeding and thrombocytopenia and/or suspected plt abnormalities due to cardiopulmonary bypass circuit

		• Inherited (Wisott-Aldrich syndrome, Bernard Soulier syndrome, Glanzmann thrombosthenia) • Any platelet count
A7	34 (3.5)	**Prophylaxis for surgery** Invasive procedures: • Liver biopsy, diagnostic endoscopy, transbronchial biopsy, laparotomy, vascular invasive procedures, other major procedures • Epidural anesthesia • Platelet count <50
A15	32 (3.3)	**Therapeutic** • Major elective non-neuraxial surgery or procedures associated with major blood loss > 500 ml (up to 48 hours post-op) • Platelet count <50
A9	24 (2.5)	**Prophylaxis for Surgery** • Major non-neuraxial surgery or procedures • Platelet count <50
A4	6 (0.6)	**Prophylaxis for Surgery** Invasive Procedures: • Central venous catheter placement • Platelet count <20
A14	5 (0.5)	**Therapeutic** • Non-CNS bleeding WHO grade 4 or neuro/ocular bleeding or up to 1 month after ICH • Platelet count <100
A10	4 (0.4)	**Prophylaxis for Surgery** • Neuro or ocular surgery (exception: cataract surgery) • Platelet count <100
A6	4 (0.4)	**Prophylaxis for Surgery** Invasive Procedures: • Lumbar puncture • Platelet count <50
A11	3 (0.3)	**Therapeutic** • Immune Thrombocytopenia, serious bleeding (WHO grade 4) • Platelet count <50 (non-ICH), <100 (ICH)
A15.5	3 (0.3)	**Therapeutic** • Minor bleeding during surgery (non-cardiac, non-neuro) • Platelet count <30
A16	3 (0.3)	**Therapeutic** • Neuro or ocular surgery (exception: cataract surgery) (up to 48 hours post-op) • Platelet count <100
A17	2 (0.2)	**Prophylaxis** • Therapeutic anticoagulation that cannot be stopped • Platelet count <30
Inappropriate (N=701)		
I1	370 (52.8)	**Prophylaxis for spontaneous bleeding** Non-immune thrombocytopenia • Hypoproliferative thrombocytopenia due to hematologic malignancies, hematopoietic cell transplant or cytotoxic chemotherapy, sepsis or medication induced • Platelet count >10
I15	72 (10.3)	**Therapeutic** • Major elective non-neuraxial surgery or procedures associated with major blood loss > 500 ml (up to 48 hours post-op)

		• Platelet count ≥50
I12	62 (8.8)	**Therapeutic** • Non - CNS bleeding WHO grade 2 • Platelet count ≥30
I13	47 (6.7)	**Therapeutic** • Non- CNS bleeding WHO grade 3 • Platelet count ≥50
I11.5	33 (4.7)	**Therapeutic** • Prophylactic transfusion for ITP • Any platelet count, any dose
I18	33 (4.7)	**Therapeutic** Patients with platelet dysfunction and WHO grade < 2 bleeding: • Acquired i.e. antiplatelet agents, myeloproliferative disorders, aplastic anemia • Cardiac surgery patients (n=31) with perioperative bleeding and thrombocytopenia and/or suspected plt abnormalities due to cardiopulmonary bypass circuit • Inherited (Wisott-Aldrich syndrome, Bernard Soulier syndrome, Glanzmann thrombosthenia) • Any platelet count
I9	21 (3.0)	**Prophylaxis for surgery** Invasive procedures: • Major non-neuraxial surgery or procedures • Platelet count ≥50
I7	19 (2.7)	**Prophylaxis for surgery** Invasive procedures: • Liver biopsy, diagnostic endoscopy, transbronchial biopsy, laparotomy, vascular • Invasive procedures, other major procedures • Platelet count ≥50
I15.5	17 (2.4)	**Therapeutic** • Minor bleeding during surgery (non-cardiac, non-neuro) • Platelet count ≥30
I11	10 (1.4)	**Therapeutic** • Immune Thrombocytopenia, serious bleeding (WHO grade 4) • Platelet count ≥50 (non-ICH), ≥ 100 (ICH)
I4	5 (0.7)	**Prophylaxis for surgery** Invasive procedures: • Central venous catheter placement • Platelet count ≥20
I17	4 (0.6)	**Prophylaxis** • Therapeutic anticoagulation that cannot be stopped. • Platelet count ≥30
I16	3 (0.4)	**Therapeutic** • Neuro or ocular surgery (exception: cataract surgery) (up to 48 hours post-op) • Platelet count ≥100
I6	2 (0.3)	**Prophylaxis for Surgery** • Lumbar puncture • Platelet count ≥50
I8	2 (0.3)	**Prophylaxis for Surgery** • Epidural anesthesia • Platelet count ≥80
I10	1 (0.1)	**Prophylaxis for Surgery**

		• Neuro or ocular surgery (exception: cataract surgery) • Platelet count ≥100
Indeterminate (N=17)		
IND	17 (1.0)	• Unable to adjudicate; not enough information provided

Table 5.1.12. The frequency of the various reasons for orders of platelets that were deemed "appropriate", "inappropriate" or "indeterminate."

Table 5.1.13. Breakdown of Top 3 Inappropriate Categories by Hospital Classification [Number (%) of orders by inappropriate classification]

Community Hospital- Adult orders

Code	Code Description	# of orders (% of inappropriate) N=435
I1	**Prophylaxis for spontaneous bleeding** Non-immune thrombocytopenia • Hypoproliferative thrombocytopenia due to hematologic malignancies, hematopoietic cell transplant or cytotoxic chemotherapy, sepsis or medication induced • Platelet count >10	259 (59.5)
I12	**Therapeutic** • Non - CNS bleeding WHO grade 2 • Platelet count ≥30	38 (8.7)
I15	**Therapeutic** • Major elective non-neuraxial surgery or procedures associated with major blood loss > 500 ml (up to 48 hours post-op) • Platelet count ≥50	31 (7.1)

Teaching Hospitals Adult orders

Code	Code Description	# of orders (% of inappropriate) N=266
I1	**Prophylaxis for spontaneous bleeding** Non-immune thrombocytopenia • Hypoproliferative thrombocytopenia due to hematologic malignancies, hematopoietic cell transplant or cytotoxic chemotherapy, sepsis or medication induced • Platelet count >10	111 (41.7)
I15	**Therapeutic** • Major elective non-neuraxial surgery or procedures associated with major blood loss > 500 ml (up to 48 hours post-op) • Platelet count ≥50	41 (15.4)
I18	**Therapeutic** Patients with platelet dysfunction and WHO grade < 2 bleeding: • Acquired i.e. antiplatelet agents, myeloproliferative disorders, aplastic anemia • Cardiac surgery patients with perioperative bleeding and thrombocytopenia and/or suspected plt abnormalities due to cardiopulmonary bypass circuit • Inherited (Wisott-Aldrich syndrome, Bernard Soulier syndrome, Glanzmann thrombosthenia) Any platelet count	27 (10.2)

Table. 5.1.14. Significance of differences in the absolute number of orders deemed "appropriate" and "inappropriate" in hospitals with and without measures in place for promoting appropriate ordering practices.

Measure assessed	Result	All Hospitals		Community		Teaching	
		Yes	No	Yes	No	Yes	No
Guidelines	A*	562	402	345	234	217	168
	I*	372	316	236	186	236	130
	Total	984	718	581	420	453	298
	P value	0.0875		0.2465		0.1877	
Pre-printed order sets	A	**171**	**337**	NC*		NC*	
	I	**70**	**272**				
	Total	**241**	**609**				
	P value	**<0.0001**					
Computerized Physician Order Entry (CPOE)	A	219	437	**94**	**305**	125	132
	I	168	295	**95**	**206**	73	89
	Total	387	732	**189**	**511**	198	221
	P value	0.3151		**0.0185**		0.5394	
Prospective Order Screening	A	**330**	**326**	**176**	**223**	154	103
	I	**197**	**272**	**88**	**219**	109	53
	Total	**527**	**598**	**264**	**442**	263	156
	P value	**0.0060**		**<0.0001**		0.1296	
Audit and Feedback	A	173	481	84	313	89	168
	I	106	365	53	245	53	109
	Total	279	846	137	558	142	277
	P value	0.1963		0.2691		0.6869	

**A-Appropriate*
**I-Inappropriate*
**NC-Not calculated*

Table 5.1.14. Summarizes the statistical analysis of the effectiveness of various measures intended to facilitate appropriate ordering of platelets for transfusion. The calculations are based upon the total "appropriate" and "inappropriate" numbers of platelet transfusions ordered for each specific measure by all hospitals indicating their use (or not) of that particular measure, and separately for Community hospitals and Teaching hospitals. For each measure within each hospital classification ("All", "Community" and Teaching") the number of orders deemed "Appropriate" and "Inappropriate" together with the total for each grouping is displayed. The P value is included for each set of results. Those combinations of hospital classification and screening measure showing statistically significant effect are highlighted in bold font. A Chi^2 test was used to determine statistical significance.

"Guidelines", widely reported to be in place at most hospitals, appear in and of themselves to have no significant benefit. Similarly, while not widely used, "Audit and Feedback" as being practiced also appears of little value. However, the use of "Pre-printed Order Sets" appears highly effective in all hospital settings. "Prospective Order Screening" appears to be useful in Community hospitals but appears strangely ineffectual as applied in Teaching hospitals. Similiarly, "Computerized Physician Order Entry (CPOE)" appears of small benefit in Community hospitals but without benefit as used in Teaching hospitals.

5.2 Audit Results for Pediatric/Neonatal Platelet Orders (patients ≤18 years of age)

Audit results in this section will not be as detailed as the "Adult" platelet orders as the platelet order numbers were not sufficient for detailed statistical analysis.

Table 5.2.1. Physician Specialty ordering platelets by hospital classification

Specialty ordering platelets	Total # (%)	Community # (%)	Teaching # (%)
Hematology/Oncology	76 (36.2)	0 (0.0)	76 (42.0)
Internal Medicine	54 (25.7)	15 (51.7)	39 (21.5)
Neonatology	38 (18.1)	2 (6.9)	36 (19.9)
Hematology	14 (6.7)	4 (13.8)	10 (5.5)
Oncology	9 (4.3)	4 (13.8)	5 (2.7)
Emergency Medicine	9 (4.3)	1 (3.4)	8 (4.4)
Surgery	3 (1.4)	0 (0.0)	3 (1.7)
Other	3 (1.4)	3 (10.3)	0 (0.0)
Unknown	2 (1.0)	0 (0.0)	2 (1.1)
Cardiology	1 (0.5)	0 (0.0)	1 (0.6)
Critical Care	1 (0.5)	0 (0.0)	1 (0.6)
Total	210	29	181

Table 5.2.1. The Top 3 specialties for pediatric platelet orders were Hematology/Oncology representing 36.2% (76/210) orders; Internal Medicine representing 25.7% (54/210) orders and Neonatology 18.1% (38/210) orders.

Table 5.2.2. Hospital location to which platelet orders were issued for transfusion by hospital classification.

Platelet Issued to	Total # (%)	Community # (%)	Teaching # (%)
Inpatient-Other	107 (50.9)	8 (27.6)	99 (54.7)
Outpatient-Oncology, Hematology, Other	52 (24.8)	16 (55.2)	36 (19.9)
Inpatient-ICU	35 (16.7)	1 (3.4)	34 (18.8)
Emergency	8 (3.8)	1 (3.4)	7 (3.9)
Operating room	4 (1.9)	0 (0.0)	4 (2.2)
Other	4 (1.9)	3 (10.3)	1 (0.6)
Pediatric/Neonatal Total	210	29	181

Table 5.2.2. Presents the location within the hospitals to which platelets were issued and where transfusion of platelets was assumed to have taken place. Inpatient-Other and Outpatient (Oncology, Hematology, Other) categories were 50.9% and 24.8% respectively of all the platelet doses transfused (patient age≤18). The next most frequent areas for platelet transfusion were Inpatient-ICU (16.7%) and Emergency department (3.8%). Outpatient (Oncology, Hematology, Other) category represented 55.2% of platelet orders at Community Hospitals compared to 19.9% of platelet orders at Teaching hospitals.

Table 5.2.3. Clinical/Transfusion Indication for Platelets.

Transfusion Indication	Total # (%)	Community # (%)	Teaching # (%)
Prophylactic (non-bleeding, no procedure)	178 (84.8)	28 (96.6)	150 (82.9)
Therapeutic (currently bleeding)	28 (13.3)	1 (3.4)	27 (14.9)
Pre-procedure (before invasive procedure)	4 (1.9)	0 (0.0)	4 (2.2)
Pediatric/Neonatal Total	210	29	181

Table 5.2.3. Presents the clinical indication for platelet transfusion orders. Prophylactic (non-bleeding, no procedure) represents 84.8% of platelet orders while therapeutic (currently bleeding) and Prophylactic (before invasive procedure) represent 13.3% and 1.9% respectively for All hospitals.

Table 5.2.4. Bleeding status for Platelet transfusions in Therapeutic (currently bleeding) category

Bleeding status (currently bleeding)	Total # (%)	Community # (%)	Teaching # (%)
Major bleed (WHO Grade 3-4)*	6 (21.4)	1 (100.0)	5 (18.5)
Minor bleed (WHO Grade 1-2)*	22 (78.6)	0 (0.0)	22 (81.5)
Pediatric/Neonatal Total	28	1	27

*(Miller et al., 1981)

Table.5.2.5. Pre-transfusion Platelet counts

Pre-transfusion platelet counts	Total # (%)	Community # (%)	Teaching # (%)
No platelet count	3 (1.4)	0 (0.0)	3 (1.7)
≤ 10*	44 (21.0)	13 (44.8)	31 (17.1)
11-25	61 (29.0)	13 (44.8)	48 (26.5)
26-50	69 (32.9)	2 (6.9)	67 (37.0)
51-99	22 (10.5)	0 (0.0)	22 (12.2)
≥100	11 (5.2)	1 (3.4)	10 (5.5)
Pediatric/Neonatal Total	210	29	181

**5 platelet orders with pre-transfusion platelet counts ≤10 were for ITP patients (non bleeding, no planned procedure); all deemed inappropriate.*

Figure 5.5

Pediatric/Neonatal orders (patients ≤ 18 years old) n=210

Overall classification of Pediatric/Neonatal platelet transfusion orders. Of the 210 orders for platelets, 68 (33.0%) were classified as appropriate while 133 (63.0%) were deemed inappropriate and 9 (4.0%) were indeterminate.

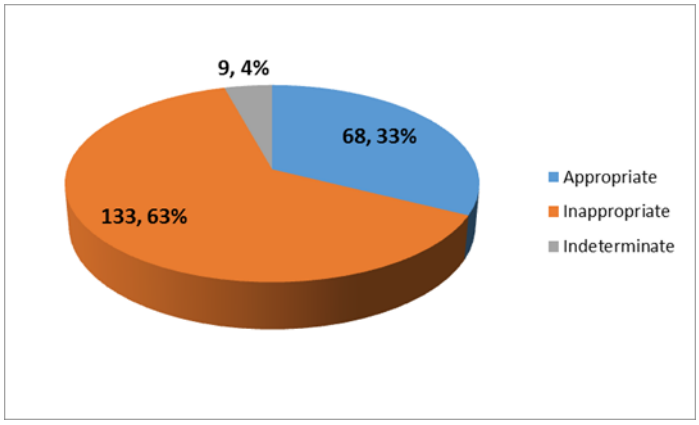


Table 5.2.6. Appropriateness/inappropriateness by Hospital classification

Hospital classification	Appropriate (%)	Inappropriate (%)	Indeterminate (%)	Total
Community	14 (48.3)	14 (48.3)	1 (3.4)	29
Teaching	54 (29.9)	119 (65.7)	8 (4.4)	181
Total	68 (32.4)	133 (63.3)	9 (4.3)	210

Table 5.2.6. The proportion of pediatric platelets orders deemed “appropriate”, “inappropriate” or “indeterminate” by hospital class, number and percentage.

Table 5.2.7. Appropriateness/inappropriateness based upon issued location (Ranked by highest inappropriate % to lowest)

Platelet Issued to	Appropriate # (%)	Inappropriate # (%)	Indeterminate # (%)
Inpatient-Other	33 (30.8)	73 **(68.2)**	1 (1.0)
Inpatient-ICU	10 (28.6)	23 **(65.7)**	2 (5.7)
Emergency	2 (25.0)	5 **(62.5)**	1 (12.5)
Outpatient-(Oncology, Hematology, Other)	20 (38.5)	29 **(55.8)**	3 (5.8)
Other	2 (50.0)	2 **(50.0)**	0 (0.0)
Operating room	1 (25.0)	1 **(25.0)**	2 (50.0)

Table 5.2.8. Pre-transfusion platelet counts and appropriateness

Pre-transfusion platelet counts	Appropriate # (%)	Inappropriate # (%)	Indeterminate # (%)
≤ 10	39 (88.6)	5 (11.4)	0 (0.0)
11-25	12 (19.7)	48 (78.7)	1 (1.6)
26-50	14 (20.3)	53 (76.8)	2 (2.9)
51-99	1 (4.5)	19 (86.4)	2 (9.1)
≥100	1 (9.1)	8 (72.7)	2 (18.2)
No platelet count	1 (33.3)	0 (0.0)	2 (66.7)
Total	68	133	9

Table 5.2.8. For pre-transfusion platelets ≤$10x10^9$/L, 88.6% (39/44) of the platelet orders were deemed appropriate, for platelet counts >$10x10^9$/L, 17.2% (28/163) orders were deemed appropriate.

Table 5.2.9. Major transfusion indication - appropriate/inappropriate/indeterminate

Transfusion Indication	Appropriate # (%)	Inappropriate # (%)	Indeterminate # (%)
Prophylactic (non-bleeding, no procedure)	51 (28.7)	120 (67.4)	7 (3.9)
Therapeutic (currently bleeding)	14 (50.0)	12 (42.9)	2 (7.1)
Pre-procedure (before invasive procedure)	3 (75.0)	1 (25.0)	0 (0.0)
Total	68	133	9

Table 5.2.9. For prophylactic (non-bleeding, no procedure) category, 28.7% (51/178) of the platelet orders were deemed appropriate; for Therapeutic (currently bleeding), 50.0% (14/28) of the platelet orders were appropriate and for Prophylactic (before invasive procedure), 75.0% (3/4) platelet orders were deemed appropriate.

Table 5.2.10. Principal Indications Leading to Appropriate / Inappropriate Platelet Transfusion in Pediatric Patients.

Code	# of orders (%)	Code Description
Appropriate N=68		
A1	27 (39.7)	**Prophylaxis for spontaneous bleeding** Non-immune thrombocytopenia • Thrombocytopenia due to hematologic malignancies, hematopoietic cell transplant, cytotoxic chemotherapy, sepsis or medication induced • Platelet count ≤$10x10^9$/L
A17	8 (11.8)	**Prophylactic** • Therapeutic anticoagulation that cannot be stopped • Platelet count <$30x10^9$/L
A12	7 (10.3)	**Therapeutic** • Non - CNS bleeding (WHO grade 2) • Platelet count <$30x10^9$/L

A-No code	8 (11.8)	• Pediatric hematologists determined platelet order was appropriate however the order did not fit into specific Appropriate category
nA1	6 (8.8)	**Therapeutic** Actively bleeding (WHO grade > 2) patients with platelet dysfunction: • Acquired i.e. antiplatelet agents, myeloproliferative disorders, aplastic anemia • Cardiac surgery patients with perioperative bleeding and thrombocytopenia and/or suspected plt abnormalities due to cardiopulmonary bypass circuit • Inherited (Wisott-Aldrich syndrome, Bernard Soulier syndrome, Glanzmann thrombosthenia) • Any platelet count
nA3	6 (8.8)	• Pre-term and < 7 days old • Pre non-neuraxial surgery • Concurrent coagulopathy • Previous significant hemorrhage (i.e. grade 3-4 • intraventricular or pulmonary hemorrhage) • Active Bleeding • Platelet count <50x10^9/L
A13	2 (2.9)	**Therapeutic** • Non - CNS bleeding –Major bleed (WHO grade 3) • Platelet count <50x10^9/L
A18	1 (1.5)	**Therapeutic** Actively bleeding (WHO grade > 2) patients with platelet dysfunction: • Acquired i.e. antiplatelet agents, myeloproliferative disorders, aplastic anemia • Cardiac surgery patients (n=75) with perioperative bleeding and thrombocytopenia and/or suspected plt abnormalities due to cardiopulmonary bypass circuit • Inherited (Wisott-Aldrich syndrome, Bernard Soulier syndrome, Glanzmann thrombosthenia) • Any platelet count
A4	1 (1.5)	**Prophylaxis for Surgery** Invasive Procedures: • Central venous catheter placement • Platelet count <20x10^9/L
A6	1 (1.5)	**Prophylaxis for Surgery** Invasive Procedures: • Lumbar puncture • Platelet count <50x10^9/L
nA2	1 (1.5)	Pre-term > 7 days old Neonatal Alloimmune Thrombocytopenia Platelet count <30x10^9/L
Inappropriate N=133		
I1	60 (45.1)	**Prophylaxis for spontaneous bleeding** Non-immune thrombocytopenia • Hypoproliferative thrombocytopenia due to hematologic malignancies, hematopoietic cell transplant or cytotoxic chemotherapy, sepsis or medication induced • Platelet count >10x10^9/L
I-No code	28 (21.0)	• Pediatric hematologists determined platelet order was inappropriate however the order did not fit into specific Inappropriate category
n-I1	22 (16.5)	• Term Infants • Platelet count ≥20x10^9/L
I11	8 (6.0)	**Therapeutic**

		• Immune Thrombocytopenia, serious bleeding (WHO grade 4) • Platelet count ≥50 (non-ICH), ≥ 100 (ICH)
I12	7 (5.3)	**Therapeutic** • Non - CNS bleeding (WHO grade 2) • Platelet count ≥30
I13	2 (1.5)	**Therapeutic** • Non - CNS bleeding (WHO grade 3) • Platelet count ≥50
n-I2	2 (1.5)	• Pre-term > 7 days old • Neonatal Alloimmune Thrombocytopenia • Platelet count ≥30
nI- No code	2 (1.5)	• Pediatric hematologists determined platelet order was inappropriate however the order did not fit into specific Inappropriate category (neonatal)
I4	1 (0.8)	**Prophylaxis for surgery** • Invasive procedures: • Central venous catheter placement • Platelet count ≥20
I10	1 (0.8)	**Prophylaxis for surgery** • Neuro or ocular surgery (exception: cataract surgery) • Taking antiplatelet agents • Platelet count ≥100
Indeterminate N=9		
Indeterminate	9 (4.3)	• Unable to adjudicate with information provided

5.3 Pre- and Post-Transfusion Platelet Counts

Of the 1693 Adult patient transfusion episodes, pre-transfusion platelet counts were available in all but 16 (<2%) and post-transfusion counts were obtained in 1254 or 74%. In pediatrics, pre-transfusion platelet counts were available in all but 3 (<1.5%) and post-transfusion counts were obtained in 152 or 72% of the platelet orders.

6.0 Limitations

Our audit has several limitations.

- Participating sites were asked which policies were in place including transfusion guidelines for platelets. There was no statistically significant difference in appropriateness between hospitals that had guidelines versus those sites that did not; however those with platelet guidelines may be utilizing alternative criteria for platelet transfusions that were non-concordant with the adjudication criteria. Transfusion guidelines have been shown to improve the appropriateness of blood and blood product transfusions but should be updated periodically to include current best practice research and recommendations.
- The effect of the possible application of multiple measures in combination for screening of platelet transfusion orders has not been assessed.
- Data are dependent on physician and nursing chart completion; the presence of mild bleeding or the use of anti-platelet agents may not have been recorded in the patient chart thus over-estimating rates of inappropriate transfusion practice.
- Pediatric audit criteria (other than for neonates) were based on Adult criteria in the absence of comprehensive clinical trial evidence in children. In particular, there are no data to establish the influence of fever in determining the threshold for platelet transfusion in children.

- The criteria used in this audit, based on the ICTMG (Nahirniak et al., 2015) and AABB (Kaufman et al., 2015) guidelines, do not recommend escalation of platelet count thresholds for platelet transfusion in the presence of fever. This has been common practice in the past and may influence decisions around therapeutic platelet transfusions made in this audit; consequently, higher rates of platelet transfusion deemed inappropriate may have resulted.
- 1.31% of transfusion episodes could not be adjudicated because the baseline transfusion documentation was absent.

7.0 Principal Findings and Recommendations

7.1 Principal Findings

- Sixty-nine of 150 eligible hospitals participated, comprising about 90% of platelet use in Ontario. Thus, this audit may be regarded as representative of the current platelet transfusion practices in the Province. A total of 1903 platelet transfusion orders were included, 1693 for Adult patients (age >18 yrs.) and 210 for pediatric patients (defined as age ≤18yrs).
- The adjudication criteria, compiled from recent recommendations by the American Association of Blood Banks (Kaufman et al., 2015a) and the International Collaboration for Transfusion Medicine Guidelines (Nahirniak et al., 2015), were independently evaluated and validated prior to the formal audit (Etchells et al., 2018).
- In Adults, the five specialties of physicians responsible for the majority of platelet transfusion orders were “Hematology/Oncology”, “Critical/Intensive Care”, “Hematology”, “Surgery “and “Internal Medicine”.
- The physician specialty with the lowest rate of inappropriate orders for platelet transfusion was “Hematology/Oncology” (28.6%) and the highest rate, “Anaesthesia” (75%). Between these two extremes, there was no significant statistical difference in the rates of inappropriate prescribing.
- About 60% of platelet transfusion orders were “prophylactic” for non-bleeding patients and 40% were either for patients with clinically apparent bleeding or in association with an invasive procedure or surgery.
- In Adult patients, platelet transfusion orders for Outpatients (mostly “Oncology/Hematology”) had the lowest frequency of inappropriate orders; by contrast, the highest frequency of inappropriate orders was seen in acute care settings – intensive care units, emergency departments, operating rooms and acute care beds/units.
- The rate of inappropriate platelet orders was similar in Teaching (42.2%) and Community hospitals (40.3%).
- There was no significant difference in the overall rates of inappropriate platelet transfusion orders for non-bleeding patients, patients with clinically apparent bleeding and patients treated in connection with an invasive procedure.
- The pre-transfusion platelet count was reported in all but 16 cases. The lower the platelet count the higher the rate of appropriate platelet transfusion orders.
- The presence or absence of certain practices intended to enhance the appropriateness of platelet transfusion showed variability in success rates. The use of pre-printed order sets had a statistically significant effect on the rate of appropriateness for all hospitals while the use of Computerized Physician Order Entry and Prospective order screening as currently applied had a greater impact on appropriateness at Community hospitals than Teaching hospitals.
- Orders for platelet transfusion in children (≤18yrs.) were assessed in 210 episodes, the great majority in teaching hospitals. Most (85%) were for prophylaxis in non-bleeding patients. Inappropriate transfusion orders constituted almost two-thirds of the total in teaching hospitals and about half in community hospitals. The rates of inappropriate pediatric platelet transfusion orders were similar for all clinical settings examined, but for some categories the numbers of cases are small. At all platelet count levels above $10x10^9$/L, high rates of inappropriate orders were seen.

- Of 56 hospitals reporting on availability of hospital guidelines for platelet transfusion, 9 of 16 teaching hospitals and 22 of 40 community hospitals stated they had established such guidelines. The remaining 25 hospitals indicated they did not have such guidelines in place. The presence of documented, Transfusion Committee approved guidelines is a necessary pre-condition for monitoring clinical practice.
- Potential adverse transfusion events which could be attributable to inappropriate platelet transfusion at the rate measured in this audit has been assessed. Based on the following assumptions/information:
  -Doses of platelets issued in Ontario annually (30% apheresis, 70% buffy coat pools of 4 doses) is approximately 60,000
  -"Wastage" rate, principally due to outdating provincially is 12%
  -Inappropriate transfusion rate (based on this audit) is approximately 40%,
  -The adverse reaction rates provided in Callum et al., 2016,
  -It is estimated that, had these inappropriate transfusions **NOT** been given, 2 cases of symptomatic sepsis, 1-2 cases of anaphylaxis 220 cases of febrile non-hemolytic transfusion reactions and 600 cases of minor allergic reactions would have been avoided.
- In this audit, orders for multiple doses of platelets for transfusion occurred in 13% (239/1903) of platelet orders. In the UK study, multiple-dosing for prophylactic indications accounted for the following: 57 double-doses, 9 triple doses and 3 quadruple doses totally 153 doses in all (8% of total). Seventy-two (47%) of these multiple doses were given to patients with hematological diseases. (Charlton et al.,2014)
- Twenty-nine platelet orders were for management of idiopathic thrombocytopenic purpura (ITP). Of these only 3 with major bleeding were deemed appropriate. In 20 cases the indication was "prophylactic" in the absence of bleeding and in 6 cases the indication was "currently bleeding (minor bleed)". Thus, 26 of 29 (90%) of platelet transfusions for ITP were deemed inappropriate. The use of platelet transfusion in ITP should therefore be a particular focus for practice improvement. (Neunert et al.,2011)

7.2 General Comments

- The frequency with which platelet transfusion orders in this Province-wide audit are deemed inappropriate against a set of criteria widely accepted as a reasonable guide to clinical practice is towards the high end of such audits reported from various countries (Appendix A).
- Inappropriate platelet transfusion orders are occurring in all patient groups at risk, Adult and Pediatric, for all clinical indications and in a wide range of clinical settings, in both Teaching and Community medical practice.
- Inappropriate platelet transfusions are not without cost. That cost comes in the form of hazard to the recipient from the potential adverse effects and complications of transfusion discussed briefly in the introduction to this report. There is also the financial cost; if 40% of the platelet transfusions were avoided, the savings on labour and materials alone would be about $25 million, in addition to the cost of managing any adverse effects from an unnecessary transfusion.
- A vigorous educational program, supported by active measures in transfusion services Province-wide to "vet" and control orders for transfusion in general and platelet transfusion in particular, is required as it is clear that a large number of platelet transfusions are being ordered without regard to scientifically established indications.

7.3 Recommendations

A platelet count of 10 X 10^9/L or greater usually provides adequate hemostasis in the absence of bleeding or planned invasive procedure. Platelet transfusions are associated with adverse events and risks; particularly serious is the risk of septic transfusion reaction. Considerations in the decision to transfuse platelets include the cause of the thrombocytopenia, comorbid conditions, symptoms of bleeding, risk factors for bleeding, and the need to perform an invasive procedure.

1. **Clinical Practice Recommendations**
   - Clinical Practice Recommendations for Adult platelet transfusion practice based on objective published clinical trial data and on recommendations of expert sources (American Association of Blood Banks, Kaufman et al., 2015a; International Collaborative for Transfusion Medicine Guidelines, Nahirniak et al., 2015) should be prepared and endorsed by an Ontario-based Expert Panel of Transfusion Medicine specialists. These guidelines should be distributed to all Ontario hospital Medical Directors of Transfusion Medicine and Chairpersons of hospital Transfusion Committees, with a view to endorsement by hospital Medical Advisory Committees (or equivalent) and incorporation into local hospital transfusion guidelines.
   - Clinical Practice Recommendations for Pediatric and Neonatal platelet transfusion practice based wherever possible on objective published clinical trial data and recommendations of expert sources should be prepared and endorsed by an Expert Panel drawn from Ontario-based pediatric and neonatal Transfusion Medicine specialists and distributed to the Medical Directors of Transfusion Medicine and Chairpersons of hospital Transfusion Medicine Committees of all hospitals with Pediatric medical services, with a view to endorsement by hospital Medical Advisory Committees (or equivalent) and incorporation into local hospital transfusion guidelines.
   - Specialty organizations for physicians who are likely to prescribe platelet transfusion (e.g. anesthesiology, emergency medicine, intensive care, medical imaging, and surgery) should be approached with a view to obtaining formal endorsement of the Ontario Clinical Practice Recommendations, so established.
2. **Defining reasons for current deviations from recommended practice**
   - Focus groups should be convened to examine the reasons for non-compliance with established guidelines, involving physicians, nurses, and patients. A variety of possible explanations could include unawareness of guidelines, lack of confidence in guidelines due to actual or perceived lack of firm clinical trial evidence, entrenched practice habits and fear of potential medico-legal consequences of restrictive transfusion practices.
   - The output from these focus groups should inform the educational approach to promoting appropriate clinical practice and highlighting areas in need of additional studies.
3. **Education for improvement**
   - For long-term effect, the optimal subject groups are medical students and residents in training. Appropriate educational content in undergraduate programs is required. Vigorous promotion of practice guidelines in Residency Training Programs can be made through the current “Boot Camp” transfusion medicine educational approach coordinated by the University of Toronto and distributed to all Ontario Medical schools, with assessment of knowledge outcomes (Lin et al., 2015). Recently, the self-directed online training program (Bloody Easy Lite for Physicians (http://belite.transfusionontario.org/) has been shown to be an effective, low-cost tool for enhancing physician transfusion knowledge (Lee et al., 2019). Inclusion of transfusion medicine content in Specialty Training Programs and in Royal College Fellowship candidate evaluation could provide additional incentive to improve practice related to the appropriate use of blood components and products (including platelets).
   - For established practitioners, access to Continuing Medicine Education programs for transfusion medicine can provide an opportunity for improvement. Active consultation prior to designing the optimal knowledge translation strategy is suggested. In particular, the high volume prescribing practitioners in Hematology/Oncology, although having on the whole a lower incidence of platelet transfusions deemed “inappropriate” than others, nevertheless represent potentially the highest absolute number of unnecessary platelet transfusions and thus merit particular attention.
   - Use of pre-printed order sets, computerized physician order entry and prospective order screening of platelet orders (see 4. (i) below) can provide further opportunities for educational intervention.
   - The current population of “Transfusion Safety Officers” and/or Nursing educators combined with regular competency assessments offers a potential mechanism for informing those nurses who are actively involved in transfusion practice with the necessary guideline information (with particular support for nurses providing care for hematology/oncology patients).

4. Practice improvement

- An effective system is required for pre-transfusion screening of requests/orders for platelets for transfusion, matched to the Provincial Clinical Practice Recommendations (1, above). This audit establishes that pre-transfusion screening of platelet orders as currently applied shows only a limited beneficial effect in reducing inappropriate orders for platelet transfusion. Pre-transfusion order screening by technologists can be effective, but the effectiveness may be limited by reluctance to question orders due to workload concerns, anticipation of conflict with the ordering physician, or insufficient Transfusion Service Medical Director support.
- An effective computerized physician order entry (CPOE) system is required which matches the clinical and laboratory information about the patient to the Clinical Practice Recommendations, and indicates non-compliance. Non-compliance should include an information-supported physician "over-ride" which would require the ordering physician to consider the need for the transfusion, and if the decision to proceed is made to provide the rationale for the order.
- Deviations from compliance recorded through the CPOE system would provide the data for review of non-compliant orders and offer the opportunity for an educational review in specific cases.
- Such recorded deviations also offer the opportunity for Transfusion Committee audit, which could become a requirement of the Quality Improvement Program.
- The application of pre-printed order sets in appropriate clinical circumstances offer the opportunity to enhance platelet transfusion ordering practices.
- Implementation of measures for practice improvement requires active support from the Medical Director of Transfusion Medicine, the Medical Advisory Committee (or equivalent) and Hospital Management.

5. Pediatric practice

The high rate of inappropriate platelet transfusion orders in pediatric patients revealed by this audit indicates a need for particular attention. The fact that the majority of these orders are placed in a limited number of hospital settings suggests that the number of individuals required to be involved in a knowledge translation initiative is relatively small, and perhaps more susceptible to a more limited, targeted approach.

6. Consider devolution of costs of procuring blood components and products to hospitals

Currently the costs of Canadian Blood Services in procuring and distributing blood components and products are met directly by Provinces and Territories (except Quebec) by direct funding in proportion to the issue of red cell doses to each of those Provinces and Territories. Hospitals meet the costs of transfusion practice in respect of storage, preparation of components and products and their administration but these costs are largely "buried" in the budgets for laboratories, nursing and supplies and are not specifically identified. Thus, there is no identifiable transfusion-specific cost to be considered in budgeting, and consequently in administrative scrutiny, which diminishes the attention paid to transfusion utilization and its hospital oversight. Blood is "free" at the point of consumption.
If the procurement of blood components and products by hospitals were an identifiable and material cost to the hospital, there would be an incentive to pay more attention to their use including appropriate prescribing practices. The current lack of motivation is a significant impediment to efforts to improve clinical transfusion practices. Oversight by hospital Transfusion Committees would be facilitated and more exacting pre-transfusion screening enhanced to reduce costs from inappropriate transfusion.
It is therefore recommended that the current funding model for provision of blood components and products be reviewed and the desirability of devolving costs to hospitals be assessed.

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9.0 Appendices

9.1 Appendix A.

Reference	Country	Criteria/Guidelines	Sample Size	Inappropriate	Indeterminate
Thomson et al. 1991	UK	NIH 1987	100 episodes	19%	29%
Hawkins et al. 1994	New Zealand	BCSH 1992	13 episodes	0	-
Metz et al. 1995	Australia	NIH 1987	215 episodes	12.6%	-
Cheng et al. 1996 Post intervention	Hong Kong	BCSH 1992*	999 episodes 997 episodes	22.6% 12.4%	- -
Tuckfield et al. 1997 Post intervention	Australia	NIH 1987	200 episodes	13% 2.5%	- -
Schofield et al. 2003	Australia	Aust. 2001	414 episodes	33%	-
Pentti et al. 2003	Finland	"Local"**	75 episodes	66%	-
Hui et al. 2005 Post intervention	Australia	Aust. 2001	385 episodes 444 episodes	5% 3%	8% 4%
Saluja et al. 2007	India	BCSH 2003	2093 episodes	12%	-
Charlewood 2007	New Zealand	Aust. 2001	388 epsiodes	13%	-
Qureshi et al. 2007	United Kingdom	BCSH 2003	4421 episodes	36%	16%
Ang et al. 2008	USA	"Local"**	282 episodes	11%	-
Arewa 2009	Nigeria	Unknown	682 episodes	81%	-
Sheikholeslami et al. 2012	Iran	BCSH 2003	76 episodes	40.8%	-
Lin et al. 2010	Taiwan	"Local"**	5754 episodes	30.4%	-
ANZICS	Aust. NZ	Aust. 2001	231 patients	53%	-
Natl. Comp. Audit 2010	United Kingdom	BCSH 2003	3296 episodes	27.8%	10.3%
Buhrkuhl et al. 2012	New Zealand	"Local"**	72 prophylactic 21 therapeutic	28% 33%	- -
DHSS, Victoria 2013	Australia	Aust. 2001	679 episodes	33%	-
Sonnekus et al. 2014	South Africa	SA NBS	144 episodes	34%	11.1%
Collins et al. 2014***	USA	"Local" CPOE	1102 "alerts"	58.3%	-
Solves et al. 2014	Spain	"Local"****	334 episodes	41.8%	-
Etchells et al. 2018	Canada	"Local"	200 episodes	22%	-

*Guidelines were modified version of the BCSH 1992 guidelines

** Guidelines used were institution-specific policies

***1,102 of 1,889 orders for platelets processed in a computer physician order entry system triggered an "alert" that the order did not meet guidelines.

****Guidelines of Spanish Society of Blood Transfusion; includes non-compliant with indication and/or dose.

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