Strategies to Reduce Diagnostic Blood Loss and Anemia in Hospitalized Patients: A Scoping Review

Tine François, MD[1]
Julien Charlier, MD[1]
Sylvain Balandier, MD[1]
Alix Pincivy, MLIS[2]
Marisa Tucci, MD[1]
Jacques Lacroix, MD[1]
Geneviève Du Pont-Thibodeau, MD, MSc[1]

OBJECTIVES: Blood sampling is a recognized contributor to hospital-acquired anemia. We aimed to bundle all published neonatal, pediatric, and adult data regarding clinical interventions to reduce diagnostic blood loss.

DATA SOURCES: Four electronic databases were searched for eligible studies from inception until May 2021.

STUDY SELECTION: Two reviewers independently selected studies, using predefined criteria.

DATA EXTRACTION: One author extracted data, including study design, population, period, intervention type and comparator, and outcome variables (diagnostic blood volume and frequency, anemia, and transfusion).

DATA SYNTHESIS: Of 16,132 articles identified, we included 39 trials; 12 (31%) were randomized controlled trials. Among six types of interventions, 27 (69%) studies were conducted in adult patients, six (15%) in children, and six (15%) in neonates. Overall results were heterogeneous. Most studies targeted a transfusion reduction ($n = 28$; 72%), followed by reduced blood loss ($n = 24$; 62%) and test frequency ($n = 15$; 38%). Small volume blood tubes ($n = 7$) and blood conservation devices ($n = 9$) lead to a significant reduction of blood loss in adults (8/9) and less transfusion of adults (5/8) and neonates (1/1). Point-of-care testing ($n = 6$) effectively reduced blood loss (4/4) and transfusion (4/6) in neonates and adults. Bundles including staff education and protocols reduced blood test frequency and volume in adults (7/7) and children (5/5).

CONCLUSIONS: Evidence on interventions to reduce diagnostic blood loss and associated complications is highly heterogeneous. Blood conservation devices and smaller tubes appear effective in adults, whereas point-of-care testing and bundled interventions including protocols and teaching seem promising in adults and children.

KEY WORDS: blood conservation devices; diagnostic blood loss; iatrogenic anemia; scoping review; small volume blood tube; transfusion

Anemia affects 50% of critically ill patients (adults and children) at ICU discharge (1–6), of which 30% of ICU adults also have underlying iron deficiency (7). Although the long-term consequences of this complication are still unknown in children, adult data show that anemia can persist for many months after a critical illness and is associated with fatigue and lower quality of life (7–9). Young children with iron-deficiency anemia or iron-deficiency alone are also at higher risk of adverse neurocognitive outcomes, behavioral changes, fatigue, lower exercise tolerance, and decreased quality of life, especially in young children (10–16). Iatrogenic blood loss from testing is a potentially important and modifiable contributor of ICU anemia and iron deficiency. Blood testing is essential for diagnosis and management of patients with

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critical illness; however, there is strong evidence that it is often excessive and involves considerable waste (1, 6). Although multiple strategies have been suggested to reduce unnecessary blood testing, their implementation in clinical settings remains extremely variable and limited.

The goal of this scoping review was to bundle all published neonatal, pediatric, and adult data regarding clinical interventions employed to reduce diagnostic blood sampling and waste during sampling. We aimed to assess their efficacy by looking at diagnostic blood loss, hemoglobin levels, transfusion numbers, and anemia prevalence at discharge. It was expected that the findings of this review would provide evidence-based data to support clinical practice changes aimed at lowering the prevalence of post-ICU anemia, a reduced exposure to transfusion, and fewer short- and long-term complications of anemia.

METHODS

This review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) extension for Scoping Reviews guidelines (17, 18) (**Fig. 1**) (**Supplemental Digital Content 1**, http://links.lww.com/PCC/C213).

Search Strategy

The search strategy was established by two intensivists (T.F., G.D.P.-T.) in collaboration with two medical librarians with specific training in medical literature searches. Comprehensive systematic searches included

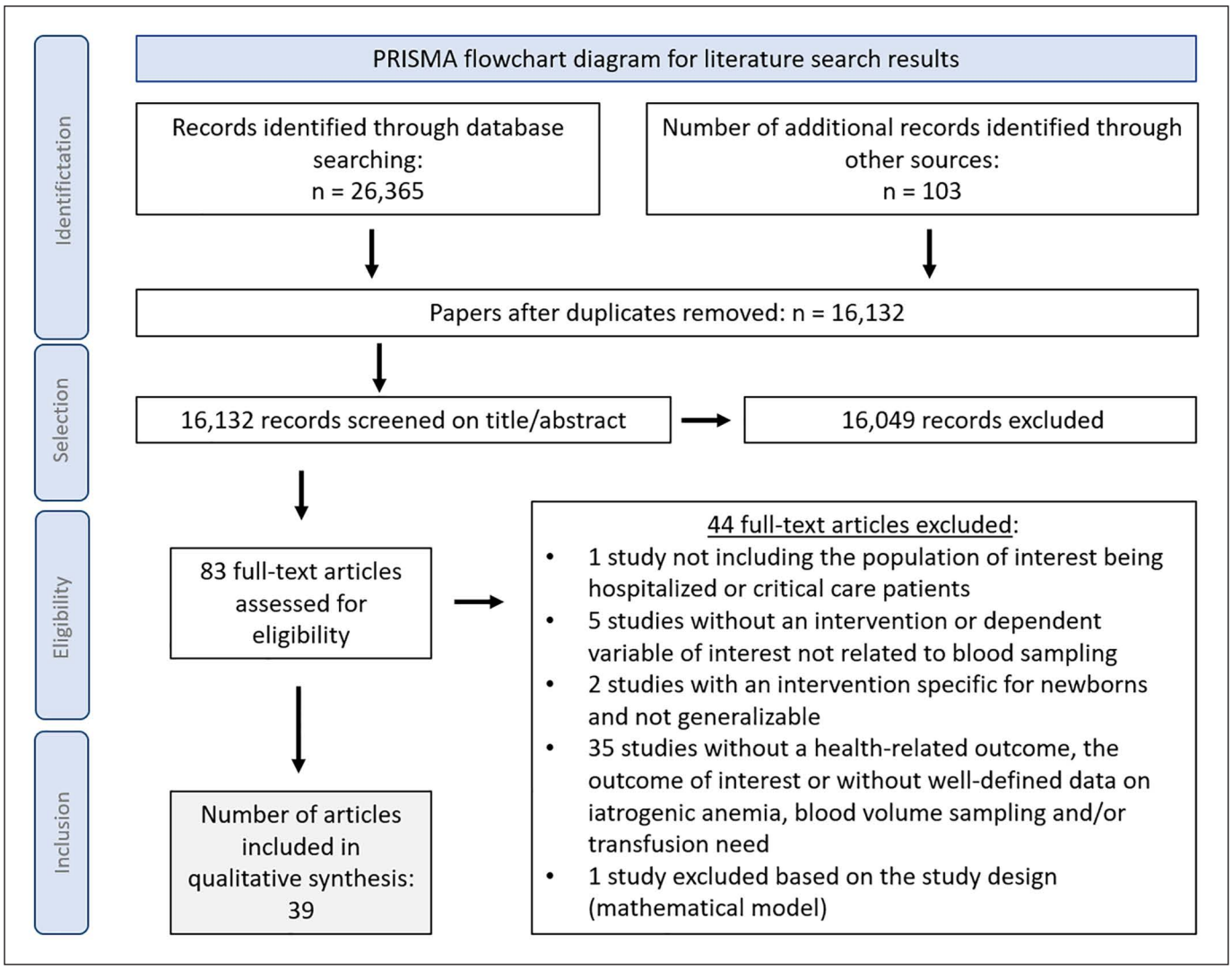

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart diagram.

articles published from inception to May 10, 2021, in the following databases: PubMed, Ovid MEDLINE, Ovid All Evidence Based Medicine Reviews, and Ovid Embase. A population, intervention, comparator, outcomes and study design strategy was used to formulate the Boolean search strategy which is detailed in the supplemental digital content (**Supplemental Digital Content 2**, http://links.lww.com/PCC/C214).

Study Selection

The selection process was conducted by three junior reviewers (T.F., J.C., S.B.) and two senior reviewers (J.L., G.D.P.-T.). Search results were independently screened on title by two reviewers (T.F., G.D.P.-T.). Abstracts from the articles retained were read independently by two reviewers (T.F., J.C.) who determined whether the article would be included or excluded. If title or abstract lacked sufficient information to allow for a decision, the article was included for further analysis. The remaining manuscripts were fully read independently by two reviewers (T.F., S.B.) to decide for inclusion or exclusion. Predefined selection criteria were used during all phases, as follows:

Population. We included studies that enrolled hospitalized pediatric patients, adult patients, and neonates. We excluded studies that evaluated palliative care patients or patients seen in outpatient clinics or in emergency departments.

Interventions and Comparators. Study interventions could include blood collection strategies (use of smaller volume tubes, closed blood sampling devices, returning blood discarded, point-of-care testing [POCT], etc.), noninvasive testing, health-care worker education, or diagnostic test prescription practice changes (protocols, decision-support systems, guidelines, …). We excluded studies assessing the impact of umbilical cord blood sampling on anemia and transfusion in neonates. This intervention is generally implemented only during the immediate postnatal period and not used in (pediatric) ICU.

The comparator could be no intervention, standard clinical practice, or another intervention.

Outcomes. The primary outcome of our review was the volume of blood loss from diagnostic testing, hereinafter referred to as "diagnostic blood loss." We planned to retain studies in which the following outcomes were assessed either as a study endpoint or at the time of discharge of death: blood volume discarded during sampling, hemoglobin levels during hospital or ICU stay, anemia incidence, or number of RBC transfusions. We excluded studies that did not include at least one of these outcomes.

Study Design. Published studies with full manuscripts whose design was observational, interventional, retrospective, or prospective were included. We excluded abstracts, posters, editorials, and letters to the editor. Previously published review articles were excluded from the analysis; references within these reviews that addressed our study objectives were identified and integrated in the discussion.

If there were discrepancies noted regarding study eligibility, this was resolved by a third senior reviewer (J.L.). Snowballing was done on the references of all full manuscripts assessed for eligibility.

Data Extraction

Following definitive selection, the following information was extracted from each study by one reviewer (T.F.) using a standardized form and summarized in a table: design, study period, population, sample size, intervention type, comparator, outcome measures and results on diagnostic blood sample volume/frequency, anemia incidence, hemoglobin levels, and transfusion. To adjust for reporting bias, the summary table was checked by two senior reviewers (G.D.P.-T., M.T.).

Risk of bias (ROB) of included randomized controlled trials (RCTs) was assessed by two independent reviewers (T.F., J.L.) using the Cochrane Collaboration ROB Tool (19). Six different domains of bias were evaluated: selection, performance, detection, attrition, reporting, and other. Three categories of ROB were considered per domain: high, unclear, or low ROB. The ROB was determined by the highest level of ROB noted for any domain. ROB in observational studies was also assessed by two independent reviewers (T.F., G.D.) using the Newcastle-Ottawa Scale (20). Three different domains of bias were evaluated: selection, comparability, and outcome. A trial was considered as of high quality when seven to nine high quality items were used. If four to six quality choices were made, the study has a high ROB, below three quality choices there is a very high ROB. Disagreements on the ROB evaluations were resolved by consensus or evaluation by a third reviewer (respectively G.D., J.L.).

We present a narrative and schematic synthesis of all included studies and their results.

RESULTS

Figure 1 is a PRISMA diagram describing the literature search and number of manuscripts retained in this scoping review. A total of 16,132 citations were identified and screened for eligibility by reading their title (first step) and abstract (second step). Eighty-three full-text articles were evaluated (third step). Forty-four studies were excluded based on predetermined exclusion criteria (Fig. 1), with 34 studies excluded because of lack of health-related outcomes or well-defined data on iatrogenic anemia (**Supplemental Digital Content 3**, http://links.lww.com/PCC/C215). Interrater reliability was high with kappa values of 0.74 for the first and second selection phase, and a kappa value of 0.96 for the selection of full texts.

The most used primary outcome was transfusion reduction (n = 28; 72%), followed by reduced blood loss volume (n = 24; 62%) and test frequency (n = 15; 38%).

Overall ROB was high in almost all included RCTs (n = 11; 92%) (**Supplemental Digital Content 4**, http://links.lww.com/PCC/C216), only the article by Rezende et al (21) was considered containing an unclear ROB. The most frequent reasons for high ROB were lack of randomization with allocation concealment and lack of blinding for the intervention and/or the outcome measure of interest. Sixteen included observational studies were of high quality, 10 observational studies have a high ROB (**Supplemental Digital Content 5**, http://links.lww.com/PCC/C217). The study from Spethmann et al (22) was the only study graded a very high ROB (22).

Table 1 summarizes the characteristics of the included studies. **Supplemental Digital Content 6** (http://links.lww.com/PCC/C218) describes the studies included in the scoping review and summarizes their results. A more detailed summary table of study results is presented in **Supplemental Digital Content 7** (http://links.lww.com/PCC/C219). We categorized studies into five categories based on intervention type (**Fig. 2**): 1) use of small volume blood collection tubes (n = 7, 18%), 2) use of a blood conservation device (BCD) (n = 9; 23%), 3) use of bedside POCT (n = 6; 15%), 4) implementation of a bundle of interventions (n = 16, 41%), and 5) other intervention (n = 1; 3%). Most studies were conducted in an adult population (27 studies, 69%); six (15%) studies reported results in a pediatric population, and six (15%) in a neonatal population.

TABLE 1.
Characteristics of Included Studies[a]

Characteristics	No. of Studies	Percentage
Publication year		
2001–2021	30	77
< 2001	9	23
Study type		
Randomized controlled trial	12	31
Randomized cross-over study	1	3
Case-control study	2	5
Prospective cohort study	17	44
Retrospective cohort study	7	18
Study setting		
Medical ICU	11	28
Surgical ICU	5	13
Cardiac ICU	1	3
Hospitalized adults (non-ICU)	5	13
Mixed adult setting	5	13
PICU	1	3
Cardiac PICU	4	10
Hospitalized children (non-ICU)	1	3
Neonatal ICU	6	15
Intervention type		
Small volume collection tubes	7	18
Blood conservation device/ Closed blood sampling	9	23
Point-of-care testing	6	15
Bundle (including education, protocols, decision-algorithms)	13	33
Bundle (without education, protocols, decision-algorithms)	3	8
Other	1	3
Outcome of interest		
Blood sample volume	24	62
Number of laboratory tests	15	38
Anemia	2	5
Hemoglobin values	11	28
Transfusion	28	72
Total	39	100

[a]One study can have more than one outcome of interest.

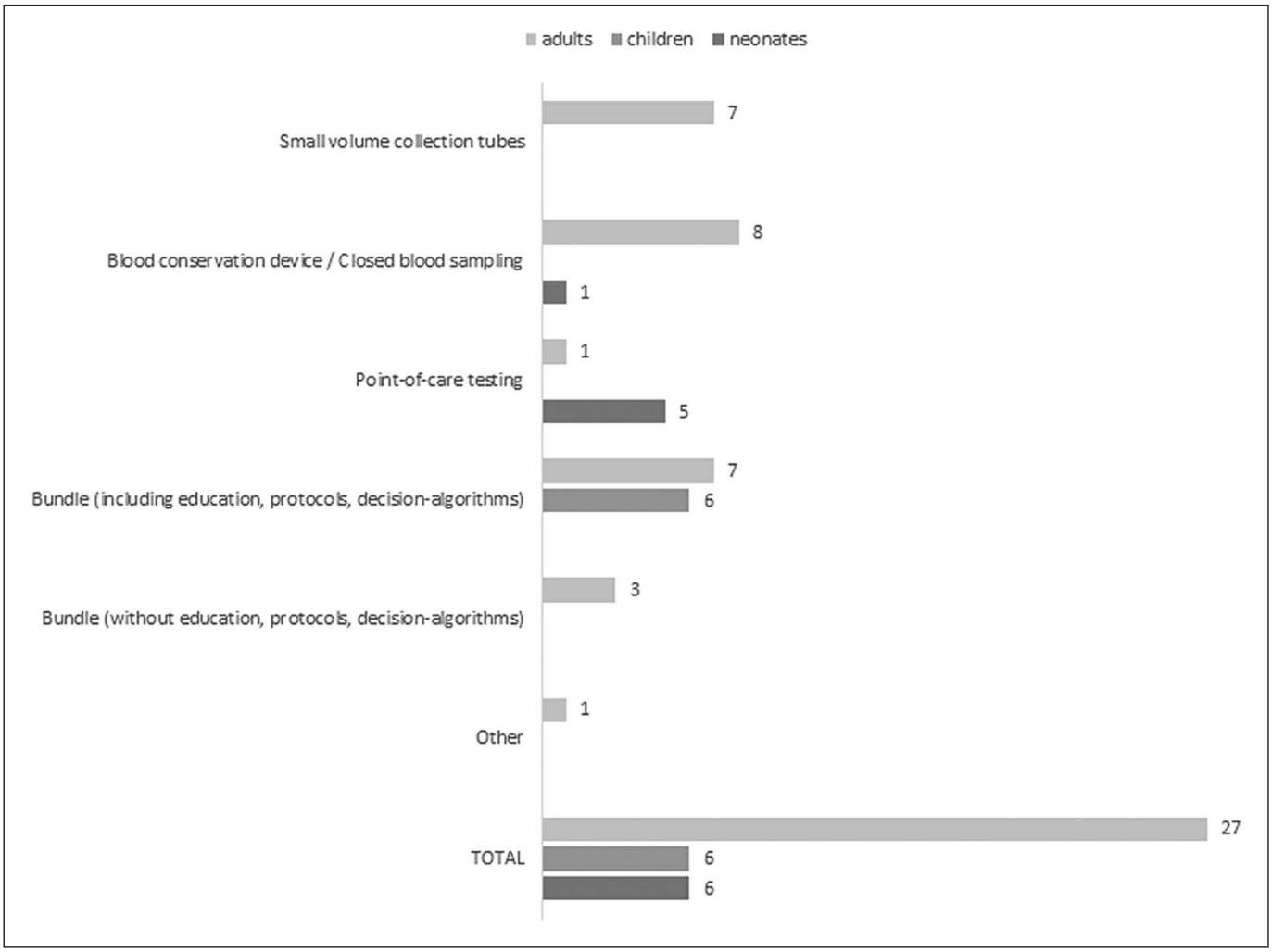

Figure 2. Studies per intervention type.

The most used primary outcome was transfusion reduction (n = 28; 72%), followed by reduced blood loss volume (n = 24, 62%) and test frequency (n = 15, 38%). Overall, 18 of 28 studies reported a reduction in transfusion compared with the control population, 22 of 24 a reduction in blood loss volume, and eight of 15 a reduction in test frequency. The effect of using smaller blood collection tubes (standard, commercially available) was evaluated in seven studies. All of these studies were conducted in adult patients only (22–28). Only the most recent study conducted by Barreda Garcia et al (23) was an RCT. Five studies reported a significant reduction of 40–47% in blood loss (22, 24, 26, 28), up to a 74% reduction (27). Four studies evaluated the effect on hemoglobin decline or transfusion (17, 20, 22, 23): only two observed a significant difference between the intervention and control group (23, 24). Spethmann et al (22) found opposing results in their study population: although the use of small-volume blood tubes clearly reduced transfusion in ICU patients, they observed a slight increase in transfusion in geriatric inpatients.

Seven research groups evaluated the use of an arterial closed blood sampling device in adult patients: one was a pre-post trial with a subgroup analysis published subsequently (29, 30), one was a prospective crossover study (31), and five were RCTs (21, 32–35). Four studies compared diagnostic blood loss with the venous-arterial blood management protection (VAMP) device versus standard blood sampling (31–34). They reported a statistically significant lower blood volume discarded with the intervention. The effect on hemoglobin concentration and transfusion was highly heterogeneous. Although three studies did not observe a statistically significant decrease in hemoglobin concentration (33–35), one study reported a statistically significant hemoglobin decline in their control patients compared with those with the VAMP device

(Δhemoglobin = –21.3 ± 23.2 g/L vs –14.4 ± 20.8 respectively, $p = 0.02$) (30). Another study similarly observed a significant difference in final hemoglobin between both groups (VAMP hemoglobin 104 ± 23.7 to 97 ± 13 g/L vs controls hemoglobin 105 ± 22.4 to 91 ± 18.0g/L; $p = 0.006$) (21). Only two studies observed a significant decrease in transfusion number in the intervention group (30, 33). One similar study in neonates observed a significantly lower transfusion volume when returning hemodiluted discarded blood with the ErythroSave device (ErythroSave, Tel Aviv, Israel) (a disposable sterile syringe which avoids the blood to cloth) (36).

Six studies looked at the effect of bedside POCT with a marked heterogeneity in the type of tests used (37–42). Overall, diagnostic blood volume was reduced with POCT compared with controls (38–40, 42). Three studies conducted in neonates also observed a significant reduction in transfusion volume or number (37, 38, 42). Weber et al (41) reported a significant reduction in diagnostic blood volume and transfusion with POCT in adults.

In a prospective cohort study, Low et al (43) observed a significantly higher blood volume drawn for diagnostic reasons in adult surgical and medical patients with an arterial line as opposed to those without one.

The remaining 16 studies implemented more than one intervention (44–59). Six pediatric studies used staff education and/or feedback, decision algorithms, or guidelines to modify the blood collected in volume and/or frequency, in combination with one or several other interventions (45, 46, 50, 52, 56, 59). All these studies observed a transfusion reduction with the intervention bundle. Studies conducted in adults observed more heterogeneous effects of the implemented bundles. Although almost all bundles lead to a decrease in blood test frequency and volume in adults (44, 47, 49, 51, 53, 54, 57, 58) only three studies observed a significant reduction in transfusion (47, 48, 57).

DISCUSSION

This scoping review summarizes current evidence on practical interventions to lower diagnostic blood loss and decrease the anemia incidence and associated transfusion in hospitalized patients. The quality of the available evidence is low to moderate with results that are very heterogeneous and sometimes conflicting. Several studies reported that the use of small-volume tubes and/or a closed-loop sampling devices may be effective in an adult population, whereas POC testing showed to be effective in the neonatal population. Intervention bundles that include educational methods with protocols or decision algorithms seem to have a positive effect on the reduction of diagnostic blood loss and related complications in both critically ill children and adults.

Reducing blood loss from diagnostic testing is an important component of patient blood management (PBM) programs. This concept was launched in 2011 by the World Health Organization to reduce anemia and avoid unnecessary blood transfusions in critically ill patients (60). The aim is to implement a patient-centered comprehensive anemia detection and management plan that involves maintaining physiologically tolerated hemoglobin concentrations, optimizing hemostasis, minimizing iatrogenic or unnecessary blood loss as well as institution of transfusion decision-making algorithms (9). Minimizing diagnostic testing seems an easily applicable aspect of PBM with a potentially important beneficial impact on long-term outcome.

This review brings to light that reducing diagnostic blood sampling is still a challenge for clinicians. Numerous studies have been conducted to evaluate interventions to lower blood test frequency, many of which did evaluate other health-related outcomes of interest, such as anemia, hemoglobin level, and transfusion requirement. We identified a total of 39 studies that assessed the implementation of various types of interventions to reduce diagnostic blood sample volume or frequency. Some interventions, such as the use of small volume or pediatric tubes, have shown a great impact in the adult population. These tubes have not been studied in children as they are already part of general routine use. Limiting blood sampling volumes remains an important challenge, especially in small children and infants, but the use of POCT, microtubes, or minimal blood sample volumes per test can all involve an improvement in those patient groups.

Although other reviews have been conducted on this topic (61–64), this is the first review that targets evidence in children, neonates as well as adults and comprises the highest number of studies and most recent evidence. Our findings are consistent with those of the systematic review undertaken by Whitehead et al (64) who reported that the use of blood conservation systems can reduce the volume of blood wasted during

diagnostic laboratory testing, but with variable effects on anemia and transfusion. Page et al (62) arrived at a similar conclusion but did not search, appraise, and/or summarize evidence in a systematic manner. The role of clinical staff education, audits, and feedback to lower laboratory test ordering and/or costs was emphasized in a narrative review by Eaton et al (61), but they only focused on adult studies.

Our review summarizes the available evidence pertaining to interventions that could be used to lower diagnostic blood loss, anemia, and transfusion in a systematic, standardized, and thorough manner. A limitation of our review is that our research question was very broad and aimed to evaluate all possible interventions regarding diagnostic blood sampling in three very different populations of hospitalized patients (adults, children, neonates). This complicates comparison between studies, although it provides a more complete summary of current evidence with some of these interventions that can be implemented in all three populations. Comparing/combining bundles of interventions was challenging due to a high degree of heterogeneity in the elements included in each bundled intervention. Another limitation is that the design of the studies retained was very heterogeneous with none being truly free from potential ROB. Many studies were only observational with lack of full reporting on the differences before and after intervention implementation. Although we identified and retained 12 RCTs, they had a potential ROB including poor randomization methods, poor description of patient attrition, and inappropriate blinding of patients, medical, and research team. It is difficult to insure complete double blinding when ascertaining blood sampling and assessing the need for transfusion. Blinding of the patient and medical team for interventions and outcome measures is almost impossible, which makes interpretation of the results very difficult.

Some studies reported other health-related outcomes and showed no increase in adverse events such as sepsis or mortality and similar or shorter lengths of ICU and hospital stay (29, 30, 32–34, 36, 41, 44, 48, 49, 57). We were unable to evaluate the effect of quality improvement interventions on costs or other outcomes in our analysis. It is known that some BCDs and smaller blood tubes are more expensive. It has been reported that a reduction of laboratory tests ordered and/or executed can lead to a reduction in anemia with less possible short- and long-term complications, a lesser need for blood products, lower morbidity and mortality, or a shorter ICU/hospital stay, which would all lead to reduced costs (44, 65–68). However, we can only assume that the implementation of a full PBM program (including diagnostic blood sampling interventions) would lead to substantial benefits.

The push-pull sampling method is another promising blood conservation method to avoid blood wasting during sampling. Its effect on diagnostic blood loss, anemia, and transfusion remains unclear as current studies are focused on the validity of laboratory results on blood sampled by using this method compared with standard blood sampling (69–73).

Future studies should focus on patient groups that are frequently sampled to identify effective interventions more easily. Many ICUs have already implemented the use of small volume tubes and/or BCDs. Clinicians working in PICUs should try to focus on minimal blood sample volumes, microtubes and POCT. Based on the available literature, clinicians should focus on implementing a PBM program in their unit including staff education, feedback on prescription behavior, information on minimal volumes and costs, and decision algorithms guiding the clinician to choose wisely when prescribing blood tests. Further research on this subject including the combination of practical and educational interventions should continue to possibly improve current PBM programs.

CONCLUSIONS

PBM programs are increasingly being implemented by clinicians to avoid the complications of anemia and transfusion. This scoping review summarizes current evidence on quality improvement interventions to reduce blood loss from diagnostic testing, anemia, and transfusion. The trials identified are highly heterogeneous, and solid evidence is lacking. Small-volume tubes and BCDs appear effective in the adult population. POCT and bundled interventions, including staff education, seem promising in the adult and pediatric population.

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1 *Division of Pediatric Critical Care Medicine, Department of Pediatrics, Centre Hospitalier Universitaire Sainte-Justine, Université de Montréal, Montréal, QC, Canada.*

2 *Medical Library, Centre Hospitalier Universitaire Sainte-Justine, Université de Montréal, Montréal, QC, Canada.*

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Dr. François conceptualized and designed the study, collected and extracted data, including the selection and systematic inclusion of the articles during the different phases of the scoping review. She carried out the critical appraisal of included articles, drafted the initial article, and reviewed and revised the article. Drs. Charlier and Balandier and Ms. Pincivy contributed to data collection and extraction, critical appraisal of included articles, and reviewed and revised the article. Drs. and Tucci, Lacroix, and Du Pont-Thibodeau conceptualized and designed the study, coordinated and supervised systematic data collection, extraction and summary, and critically reviewed and revised the article. All authors approved the final article as submitted and agree to be accountable for all aspects of the work.

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For information regarding this article, E-mail: genevieve.du.pont-thibodeau.med@ssss.gouv.qc.ca

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