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CLINICAL PRACTICE GUIDELINE

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Small-volume blood sample collection tubes in adult intensive care units: A rapid practice guideline

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Abstract

Background: This Intensive Care Medicine Rapid Practice Guideline (ICM-RPG) provides an evidence-based recommendation to address the question: in adult patients in intensive care units (ICUs), should we use small-volume or conventional blood collection tubes?

Methods: We included 23 panelists in 8 countries and assessed and managed financial and intellectual conflicts of interest. Methodological support was provided by the Guidelines in Intensive Care, Development, and Evaluation (GUIDE) group. We conducted a systematic review, including evidence from observational and randomized studies. Using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, we evaluated the certainty of evidence and developed recommendations using the Evidence-to-Decision framework.

Results: We identified 8 studies (1 cluster and 2 patient-level randomized trials; 5 observational studies) comparing small-volume to conventional tubes. We had high certainty evidence that small-volume tubes reduce daily and cumulative blood sampling volume; and moderate certainty evidence that they reduce the risk of transfusion and mean number of red blood cell units transfused, but these estimates were limited by imprecision. We had high certainty that small-volume tubes have a similar rate of specimens with insufficient quantity. The panel considered that the desirable effects of small-volume tubes outweigh the undesirable effects, are less wasteful of resources, and are feasible, as demonstrated by successful implementation across multiple countries, although there are upfront implementation costs to validate small-volume tubes on laboratory instrumentation.

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Conclusion: This ICM-RPG panel made a strong recommendation for the use of small-volume sample collection tubes in adult ICUs based on overall moderate certainty evidence.

KEYWORDS
blood transfusion, guidelines, ICM-RPG, intensive care, phlebotomy, rapid practice guideline, small-volume tubes

Editorial Comment
In this focused clinical practice recommendation, there is support to use small volume blood sampling tubes to limit blood waste which can contribute to anemia in intensive care unit patients.

1 | INTRODUCTION

Iatrogenic anemia from diagnostic blood loss in the hospitalized patient has been a longstanding concern, particularly for the patient in critical care.[1] Diagnostic phlebotomy is thought to contribute to the severity of anemia, the number of red blood cell (RBC) transfusions, and the need for anemia investigations to rule-out alternative causes.[2] Median diagnostic blood loss per day in the critical care setting with conventional sample collection tubes is 22 mL (interquartile range 15–31 mL).[3] Over 90% of the blood collected from patients for diagnostic testing is discarded.[4] Strategies to reduce the volume of blood removed for laboratory testing have included: small-volume sample collection tubes, blood conservation devices to reduce waste blood, bundling of tests onto a single collection tube, less frequent testing, and point of care devices using minute volumes.

In 1986, Henry et al. conducted a simple before-after study in critical care patients evaluating smaller sample collection tubes and found that testing volumes could be reduced by half.[5] Over the next three decades, further small studies were performed evaluating small-volume sample collection tubes to understand impacts on sample collection volumes, rates of rejected samples and diagnostic errors, rates of anemia, and number of RBC transfusions.[2,6–8] More recently, the "Small-Volume Tubes to Reduce Anemia and Transfusion" (STRATUS) multicenter stepped-wedge cluster randomized trial was published which compared conventional to small-volume sample collection tubes.[9]

Therefore, this Intensive Care Medicine Rapid Practice Guideline (ICM-RPG) was undertaken to provide an overview of the published evidence relevant to the use of small-volume collection tubes and to make recommendations for clinical practice informed by the evidence; and provide advice for successful implementation at the local level. Widespread introduction of small-volume tubes has been hindered by unsubstantiated concerns for increases in rejected samples for insufficient volume and erroneous laboratory results, including coagulation[10] and blood bank testing (with complex investigations required larger volumes of plasma less than 2%[11,12]), and increased risk of hemolyzed samples.[13]

2 | METHODS

The *Guidelines in Intensive Care, Development, and Evaluation* (GUIDE) group provided methodological support for this ICM-RPG.

2.1 | Panel composition

One member of the ICM-RPG steering committee was selected as methods chair (SO) and invited a clinical chair (JC) without relevant conflicts of interest (COI) as well as a co-methodologist (ZP). The chairs, along with the ICM-RPG steering committee (WA, EBC, MHM) invited clinical experts in critical care and hematology/transfusion medicine to serve as the guideline panel, striving to balance training, geographic location, career stage, and gender.[14] Two family members of previously critically ill patients who had received multiple diagnostic tests and blood product transfusions participated as patient/family representatives.

2.2 | Management of conflicts of interest

We used a standardized COI disclosure and management process for all panelists, including the chairs.[15,16] No relevant financial COIs were identified. One panel member was a lead author of the largest study on the topic (DS), and given this intellectual conflict of interest, participated in discussions as a content expert but was excluded from discussing or voting upon the guideline recommendation.

2.3 | Guideline question and outcomes

This guideline aimed to address the following PICO (Population; Intervention; Comparator; Outcome) question: (P) *In adult intensive care unit (ICU) patients, does the use of (I) small-volume blood collection tubes, compared to (C) regular-volume conventional blood collection tubes, (O) reduce blood loss and need for transfusion?* While transfusion was

identified as a critical outcome for the guideline, the panel was given an opportunity to suggest new outcomes and vote upon these to prioritize them as either "critical," "important," or "not important" for decision-making, in accordance with standard Grading of Outcomes, Assessment, Development, and Evaluation (GRADE) procedures.[17] The panel identified three critical outcomes (transfusions, health-related quality of life, and samples with insufficient quantity/quality for analysis) and eight important outcomes (change in hemoglobin concentration, days alive and out of hospital, mortality, length of stay, volume of blood sampled, total samples drawn, requirement for iron supplementation, and environmental impact). In addition, for the purposes of making a recommendation, data on acceptability, costs/resources, and staff workload were collected.

2.4 | Evidence sources and data synthesis

We updated an existing systematic review (SR) on transfusion avoidance strategies in critical care, which used electronic search strategies developed by a medical librarian.[8] These searches were re-run in Medline, EMBASE, Cochrane CENTRAL up to November 2023 (Supplementary Material). We included observational studies and randomized controlled trials (RCT) conducted in adult ICUs which compared small-volume blood collection tubes to conventional blood-collection tubes. All retrieved references were uploaded into Covidence, and subsequently screened independently and in duplicate by two reviewers (JC, SO, ZP) at the title and abstract stage, and again as full-texts, with a third reviewer resolving conflicts. For dichotomous outcomes, we calculated relative risks (RRs), odds ratios (ORs), and absolute risk differences (ARDs) as appropriate; and for continuous variables we calculated mean differences (MDs) or standardized mean differences (SMDs), all with associated 95% confidence intervals (CIs). We calculated pooled estimates using both fixed-effects and random-effects estimates, using random-effects models unless there was a concern about the risk of small-studies effects when only a small number of trials provided data for a given outcome.[18] When between-study differences prohibited data pooling, data were summarized narratively. All analyses were conducted using RevMan version 5.4.[19]

2.5 | Certainty of evidence

The methodology team used the GRADE approach to assess the certainty of evidence for each outcome.[20] Certainty of evidence was rated as high, moderate, low, or very low, based on the risk of bias of included studies, imprecision, indirectness, inconsistency, and risk of publication bias.[21–26] Individual study risk of bias was assessed using the Cochrane Risk of Bias (RoB)-2 tool for RCTs and ROBINS-I for observational studies.[27,28] We followed GRADE's recommendations for informative wording to describe the effect estimates.[29]

2.6 | Moving from evidence to recommendations

The chairs (JC, SO) led the panel through two virtual meetings, during which the evidence for the PICO question was reviewed. The panel then formulated draft recommendations for the PICO, using GRADE's Evidence-to-Decision (ETD) framework, considering the desirable and undesirable effects; variability in values and preferences; certainty of evidence; resource use; cost-effectiveness; equity, acceptability, and feasibility of the intervention.[30] Following the GRADE approach, the panel determined both the direction of the recommendation (for or against the intervention) and its strength (strong vs. conditional).[31] These meetings were recorded to accommodate panelists who were unable to attend. All panelists had a chance to comment and discuss the draft recommendation, after which the recommendations were voted upon using GRADEpro GDT software, which also allowed input on implementation, monitoring, and research priorities.[32] The panel used an 80% threshold of eligible voters to adopt a recommendation.

3 | RESULTS

3.1 | Characteristics of included studies

The updated SR search identified 1771 new references, of which 309 were duplicates and 1458 were excluded at the title and abstract level. After full-text screening, four studies were deemed appropriate for inclusion in addition to the four studies from the original systematic review (Supplementary Figure 1). In total, eight studies (one cluster RCT; two patient-level RCTs, and five observational studies) were included to inform the guideline.[9,33–38] There were 29,121 patients of which 27,411 (94.1%) originated from the STRATUS cluster RCT by Siegal et al.; we used data from the secondary analysis which included all ICU patients admitted for greater than 48 h; this larger secondary analysis included patients admitted during the COVID-19 pandemic and thus greater statistical power and generalizability.[9] The summary of included studies is presented in Table 1. Most studies had a low risk of bias for the outcome of transfusion, but two studies were judged to be at high risk due to bias in selection of the reported results, and one due to lack of adjustment for baseline confounders. Because of a highly heterogeneous design of the included studies, separate analyses were made according to study design (cluster RCT/patient-level RCTs with individual randomization/observational studies) and we summarized the results narratively (Supplementary Table 1). The full ETD framework leading to the guideline recommendation is found in Supplementary Table 2. A visual abstract is found in Supplementary Figure 2.

3.2 | Desirable effects

The use of small-volume tubes likely results in a small reduction in the proportion of patients transfused, although the results are

TABLE 1 Characteristics of the included studies.

Author (year)	Study design	Patients, *n*	Population	Intervention	Comparator	Risk of bias for outcome of transfusion (ROBINS-I/RoB-2)
Smoller (1989)	Observational (prospective/ retrospective)	248	Surgical ICU	Pediatric volume tubes (2.5–3.0 mL)	Adult volume tubes (4.5–10.0 mL)	Low
Harber (2006)	RCT, single center	49	Surgical ICU	Small-volume collection tubes (0.5–1.6 mL)	Standard volume collection tubes (3.5–5.0 mL)	High
Sanchez-Giron (2008)	Observational (prospective)	473	Not specified	Small-volume collection tubes (1.1–2.6 mL)	Standard volume collection tubes (2.7–4.9 mL)	Low
Dolman (2015)	RCT, single center	248	Surgical ICU	Small-volume collection tubes (1.8–3.5 mL)	Standard volume collection tubes (2.7–8.5 mL)	Low
Briggs (2019)	Observational (before/after)	200	Mixed ICU	Small-volume collection tubes (1.8–3.5 mL)	Standard volume collection tubes (2.7–8.5 mL)	High
Garcia (2020)	RCT, single center	318	Medical ICU	Pediatric volume tubes (0.25–6.5 mL)	Adult volume tubes (2.0–6.5 mL)	Low
Siegal (2023a)	Observational (before/after)	369	Surgical ICU	Small-volume collection tubes (1.8–3.0 mL)	Standard volume collection tubes (2.7–4.0 mL)	High
Siegal (2023b)	RCT, multi-center, cluster	27,411	Mixed ICU	Small-volume collection tubes (1.8–3.5 mL)	Standard volume collection tubes (4.0–6.0 mL)	Low

Abbreviations: ICU, intensive care unit; RCT, randomized controlled trial; ROB-2, risk of bias assessment-2; ROBINS-I, risk of bias in non-randomised studies of interventions.

limited by imprecision. In STRATUS, among patients with ICU stays 48 h or longer, there may be a slight reduction in risk of RBC transfusion (RR 0.97; 95% CI 0.9–1.04; ARD −1.02; 95% CI −3.17 to 0.98). In the patient-level RCTs, the point estimate for RBC transfusion was lower (RR 0.58; 95% CI 0.25 to 1.33; absolute risk −4.7%; 95% CI −8.4 to 3.7). Small-volume tubes likely result in fewer RBC units transfused per patient, as per the STRATUS trial −10.0 units/100 patients (95% CI −21.0 to −0.2; moderate certainty). These results are consistent with evidence that they reduce the daily blood sampling volume (mean −13 mL; 95% CI −15.7 to −10.3 mL; high certainty) and the cumulative sampling volume (mean −29.0 mL; 95% CI −40.1 to −17.9; high certainty).

The panel judged that although the difference in risk to individual patients is small and the evidence is limited by imprecision, the difference in number of blood products used cumulatively is large when viewed from a population perspective across the ICU or hospital. In STRATUS, the MD of 10 units less per 100 patients translated into almost 1500 units of blood saved during the trial when small-volume tubes were used. The panel also considered the potential for down-stream impacts not measured in the available trials, including impact on quality of life for patients experiencing fewer transfusions—a point highlighted by family member representatives. The panel also considered the beneficial effects for blood donors in having their donations more likely to be used for true clinical need rather than iatrogenic blood loss.

3.3 | Undesirable effects

Small-volume tubes do not appear to increase the number of specimens with insufficient quantity for analysis, these events were very rare in both arms, (small-volume tubes: 0.023%; conventional tubes: 0.028%; high certainty) (Supplementary Table 1), although there may be other lab-related issues not captured in the trial. Small-volume tubes likely result in little to no clinically relevant difference in change in hemoglobin concentration (moderate certainty) and do not negatively impact the length of ICU stay (high certainty). Lastly, moderate certainty evidence suggests the intervention is unlikely to impact ICU mortality.

3.4 | The certainty of evidence

The overall certainty of evidence was moderate: all outcomes were either of high or moderate certainty, although no study directly measured impacts upon patient health-related quality of life, the family representatives noted that a reduction in the number of transfusions would itself positively impact quality of life for patients and families in hospital, as transfusion was viewed as a stressful event.

3.5 | Values and preferences

The panel judged that most groups would view the tradeoffs between the desirable and undesirable effects similarly, and there would

probably be no important uncertainty or variability in values or preferences. The family representatives noted that most patients would prefer to have their blood drawn to small-volume tubes, in the absence of any other negative effects. For clinicians, the main tradeoffs related to costs and implementation are addressed subsequently.

3.6 | Balance between desirable and undesirable effects

Overall, the panel judged the balance of effects to favor small-volume tubes. Although the difference in effect was small at the patient level, taken in aggregate, they are large at the hospital and system level. No analyzed outcome favored conventional volume tubes.

3.7 | Resources and cost

We found no direct evidence comparing the costs of small versus conventional volume tubes. The STRATUS trial was conducted entirely within Canada, where the costs of the two types of tubes are identical, and the trial found the cost of implementation to be minimal. These were upfront costs related to implementation (validation and education), and maintenance after implementation was minimal, in comparison to the benefits in reduced transfusions which continue to accrue over time. The panel was less certain about the potential costs in other jurisdictions, where the price of different tubes may vary, and labs may require modification to analyze samples from small-volume tubes. No cost-effectiveness data were available, however given the high activity-based cost of per RBC transfusion (purchase cost per unit, pre-transfusion testing, crossmatch, nursing infusion costs, documentation, investigation of adverse reactions)[39] use of small-volume tubes would likely be cost effective in most centers, especially those which complex, long-stay ICU patients who have a higher risk of iatrogenic anemia.

3.8 | Equity

The panel concluded that the introduction of small-volume tubes would likely increase equity. First, patients who require more frequent blood samples and those with complex transfusion requirements may disproportionately benefit from the use of small-volume tubes (greater reduction in the total volume of blood drawn). Populations prone to lower hemoglobin levels (e.g., patients with chronic illness; nutritional deficiencies; congenital hemoglobinopathies; and premenopausal women may be disproportionately impacted by the higher sampling volumes of conventional tubes), a risk partially mitigated by the use of small-volume tubes.[40–42] Finally, a positive impact on the environment is likely: reducing the amount of materials used in tube production, reducing the volume of blood collected worldwide, and reducing the plastic waste from red cell transfusion storage containers, could result in reduced healthcare waste production.

3.9 | Feasibility and acceptability

The panel concluded that introducing small-volume tubes is probably acceptable and feasible. It is unlikely that patients and their families would choose conventional volume tubes over the smaller-volume tubes; the family representatives in the panel noted that increased large daily blood sample volumes and transfusions patients experience in the ICU can result in stress and anxiety. As an intervention, the use of small-volume tubes has face validity as a waste-avoidance strategy. The feasibility of adopting small-volume tubes was demonstrated in STRATUS, which as a stepped-wedge cluster RCT, also addressed implementation within the context of the clinical trial. Although it may not be feasible to transition to small-volume tubes in all settings, the panel noted that the evidence review included studies of small-volume tubes conducted in multiple other countries (Australia, Germany, Mexico, and US). However, in all instances, the change in practice would require investment by the organization in a change management strategy, and this is not under the direct control of intensive care physicians.

4 | RECOMMENDATION

We recommend the use of small-volume blood collection tubes over conventional blood collection tubes in adult ICUs (strong recommendation, moderate certainty evidence).

5 | JUSTIFICATION

While the evidence is limited by uncertainty, the use of small-volume tubes appears to result in small reductions in the proportion of patients transfused, and in a lower number of RBC transfusions. In aggregate over a long ICU stay, or across all patients in the ICU/hospital, these effects are large. The downsides of small-volume tubes are minimal; concerns about insufficient sample volumes appear to be rare with either tube type, although there may be issues with some specific lab tests which require higher volumes of blood. The major downside of using small-volume tubes is the staff education and implementation costs; these are likely to vary between centers and countries. In centers where the cost of tubes is similar and labs do not require changes in laboratory instrumentation, small-volume tubes are likely highly cost-effective. On this basis, the panel made a strong recommendation for the use of small-volume tubes, as they appear equally effective to conventional tubes; we did not identify any reason beyond the surmountable challenges of implementation for why conventional tubes should be used when small-volume tubes are available.

6 | IMPLEMENTATION AND RESEARCH PRIORITIES

An important aspect of implementation is explaining the rationale and value of small-volume tubes to front line staff; the tubes are slightly

different in terms of collection (slower filling) and the benefits may not be easily perceived. Understanding that saving blood during draws results in fewer transfusions, and hence nursing workload, may be motivating. For rare patients and tests (e.g., patients with multiple red cell antibodies), conventional volume tubes may still be required (or provision to collect two small-volume tubes). If these patients are identified prospectively, it may help to alleviate concerns regarding special tests which may not be amenable to small-volume tubes. It may be appropriate to use small-volume tubes outside of the ICU, although non-ICU patient populations may experience fewer blood draws and thus the benefits may be smaller; however, using conventional volume tubes and collecting more blood is unlikely to add value.

Before implementation, it is important for hospital laboratories to confirm that small-volume tubes can be used. For some centers, it may be as simple as switching the purchase order with a supplier, but for other centers, new equipment and processes may be needed, which could be costly. In STRATUS, all the trial centers were able to switch over quickly without any equipment changes or other major hurdles. Three other centers approached to participate in STRATUS had already transitioned to small-volume tubes.

Implementation may benefit from a team approach. The team should include phlebotomists, laboratory technologists, laboratory physicians, critical care nurses, nursing educators, critical care physicians, and individuals overseeing the purchasing supply chain to identify local challenges to implementation. The implementation process needs to include a brief validation to ensure adequate filling of tubes, compatibility with laboratory instrumentation, and validity of testing results, as compared to conventional volume tubes. The broad healthcare team must be provided with education to understand the benefit of utilizing tubes that fill slower—specifically understanding that the extra time at phlebotomy will reduce workload later in the patient journey for RBC transfusions. The nursing and supply chain personnel need to oversee a gradual transition to the implementation of the small-volume tubes to ensure existing stocks of standard volume tubes are not needlessly wasted.

Although the panel made a strong recommendation for the implementation of small-volume tubes for patients in ICU, the panel identified a need for ongoing research in additional areas of inquiry. Additional studies are needed to quantify the impact on patient and family quality of life metrics and patient experiences. Similarly, studies would be helpful to understand the economic and environmental impacts from small-volume tubes on the broader healthcare system. Implementation and quality improvement research could help streamline implementation efforts for hospitals that have yet to adopt small-volume tubes.

7 | DISCUSSION

This ICM-RPG systematically reviewed the RCT and observational data and found benefits for the implementation of small-volume tubes, including a reduction in RBC units transfused (10 units less per 100 patients in ICU). The panel made a strong recommendation for the implementation of small-volume sample collection tubes for patients in ICU. The undesirable effects of the small-volume tubes were found to be minimal in comparison to the benefits in terms of reducing RBC transfusions. The panel believed that the benefits outweighed the risks for most patients and that the recommendation applies to the broad ICU population. Although no cost-effectiveness analyses were available, the panel considers that the costs associated with implementing small-volume tubes would be outweighed by the benefits in terms of savings in transfusion costs at the hospital and system levels.

The guideline panel recognized the importance of a multidisciplinary team and a stepwise implementation of the small-volume tubes. The experience of the STRATUS hospital sites and many panel members that implementation was highly feasible with current laboratory analyzers. If a team member suggests the implementation is not feasible due to laboratory instrumentation, it is important to fully investigate with other sites using the same platform to understand if this conclusion is valid before abandoning implementation. Lastly, given the minimal (if any) downside to the implementation of small-volume tubes, consideration can be made for hospital-wide implementation.

8 | CONCLUSIONS

This ICM-RPG makes a strong recommendation for critical care units to implement small-volume tubes to reduce the volume of blood collected and to reduce the volume of RBC transfusions, based on overall moderate certainty evidence. The guideline panel believed that the intervention is highly likely to be acceptable to most patients and families. The guideline panel felt the benefits (reduction in RBC transfusion) were highly likely to outweigh the undesirable effects (burden of a brief implementation process). The guideline panel thought that the intervention was highly feasible and cost-effective in the vast majority of hospitals, given successful implementation at STRATUS sites across Canada and conduct of multiple studies in hospitals around the world.

AUTHOR CONTRIBUTIONS

JC, SO, and ZP conducted the systematic review, data extraction, quality review, and analysis. All authors provided input verbally and voted electronically on the guideline recommendation, All authors contributed to the drafting and approval of the final manuscript.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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