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Review paper

What blood conservation practices are effective at reducing blood sampling volumes and other clinical sequelae in intensive care? A systematic review

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ABSTRACT

Objectives: The objective of this study was to critically appraise and synthesise evidence for blood conservation strategies in intensive care. Blood sampling is a critical aspect of intensive care to guide clinical decision-making. Repeated blood sampling can result in blood waste and contamination, leading to iatrogenic anaemia and systemic infection.
Review method used: Cochrane systematic review methods were used including meta-analysis, and independent reviewers.
Data sources: A systematic search was conducted in Medline, CINAHL, PUBMED and EMBASE databases. The search was limited to randomised controlled trials (RCTs) and cluster RCTs, published in English between 2000 and 2021.
Review methods: Paired authors independently assessed database search results and identified eligible studies. Trials comparing any blood conservation practice or product in intensive care were included. Primary outcomes were blood sample volumes and haemoglobin change. Secondary outcomes included proportion of patients receiving transfusions and infection outcomes. Quality appraisal employed the Cochrane Risk of Bias tool. Meta-analysis using random effects approach and narrative synthesis summarised findings.
Results: Eight studies (n = 1027 patients), all RCTs were eligible. Six studies included adults, one studied paediatrics and one studied preterm infants. Seven studies evaluated a closed loop blood sampling system, and one studied a conservative phlebotomy protocol. Studies were of low to moderate quality. Meta-analysis was not possible for interventions targeting blood sample volumes or haemoglobin. Decreased blood sample volumes reported in four studies were attributable to a closed loop system or conservative phlebotomy. No study reported a significant change in haemoglobin. Meta-analysis demonstrated that use of a closed system (compared to open system) reduced the proportion of patients receiving transfusion [Risk Ratio (RR) 0.65, 95% CI 0.46–0.92; 287 patients] and reduced intraluminal fluid colonisation [RR 0.25, 95% CI 0.07–0.58; 500 patients].
Conclusions: Limited evidence demonstrates closed loop blood sampling systems reduced transfusion use and fluid colonisation. Simultaneous effectiveness-implementation evaluation of these systems and blood conservation strategies is urgently required.
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1. Introduction

Management of critically ill intensive care patients typically involves extensive diagnostic testing and procedures to inform clinical decision-making. Critical care clinicians are concerned about missing important clinical changes in their patients' condition, and blood sampling is one of the most frequent procedures to facilitate both point-of-care and laboratory assessments.[1] Within the intensive care setting, this is commonly facilitated by an indwelling arterial catheter (AC) connected to pressurised administration sets that maintain patency and facilitate continuous monitoring. Blood sampling via these systems is enabled but can result in blood wastage and contamination, iatrogenic anaemia, and even systemic infection.[2,3]

Anaemia is caused by a variety of factors during critical illness. Phlebotomy, sepsis, gastrointestinal bleeding, clotting disorders, blood loss from vascular procedures, renal failure, dietary deficits, bone marrow suppression, and reduced erythropoietin response are all factors that influence its severity.[4–6] For more than 40 years, medical literature has emphasised the importance of an iatrogenic contribution to anaemia in hospitalised patients as a result of blood sampling, as well as its negative impact upon recovery.[7–10] Blood draws from intravascular devices are associated with more blood loss because a clearing or 'discard' volume must be withdrawn from the device first to guarantee the sample is whole blood and not partially drug or infusion fluid. The presence of arterial or central venous catheters has been shown to contribute 2.3- to 4-fold higher median blood samples per day.[2,11] The indication for placing a vascular access device (central venous or arterial) may facilitate more efficient medical care; however, blood sampling from these is extensive and not always clinically indicated.[11] Blood sampling volumes from critically ill adult patients has been reported to be ranging from 41.5 ml to 377 ml per day.[4,6,11,12] The average daily blood sampling volumes described varied depending on the population investigated, the duration of stay evaluated, and the study methods.[13,14]

Arterial catheters are short-term vascular access devices; however, they are one of the most heavily manipulated catheters in intensive care. When the administration set is opened for blood collection, arterial catheter access puts the stopcock hub and, subsequently, the intraluminal line at risk of microbial contamination.[15] The rate of AC-related blood stream infection (AC-BSI) is comparable with rates reported for short-term central venous catheters from 0.4 to 3/1000 catheter days (for catheter-related blood stream infection [CRBSI])[3,16–18] or 3.1/1000 catheter days when applying surveillance definition[19] and significantly higher than rates reported for peripheral intravenous catheters (0.14–0.5/1000 catheter days).[17,20]

While blood testing is required to inform clinical decisions, products and practice have been developed to reduce unnecessary sampling, and the risk of iatrogenic blood loss and infection. These range from clinically indicated sampling, smaller volume tubes, use of closed systems, and consideration of alternate noninvasive point-of-care monitoring.[21] Closed systems are commonly used across many ICU settings and have been implemented because of the cross-purpose outcomes of blood conservation and infection prevention.[22–26]

Previous systematic reviews in this area have identified an apparent positive association between blood conservation products, practice and/or strategies, and blood management outcomes. However, many included studies were published pre-2000 and/or were nonrandomised (n = 18 studies).[27,28] Further, neither of these reviews analysed other clinical sequelae, such as infection-related outcomes. The aim of this systematic review was to critically appraise and synthesise all clinical outcomes from RCTs evaluating ICU blood management interventions published after the year 2000 so that the summary of findings would reflect contemporary practice and rigorous trial evaluation to represent the current state of evidence in this field.

2. Method

2.1. Research design

This review method was based on Cochrane systematic review methodology including meta-analysis.[29] The review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO, ID CRD42019137227). The systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[30]

2.2. Search strategy

The databases Medline, CINAHL, PUBMED, and EMBASE were systematically and independently searched for identification of randomised controlled trials (RCTs) between the years January 2000 and December 2021. The search strategy was developed by S.M. and S.K. with the help of a healthcare librarian and used subject headings or text words relevant to blood/sampling strategies in critical care. The search employed MeSH and textual terms related to "intensive care"; "critical care"; "blood conservat*"; "phlebotomy"; "blood sampl*"; and "randomised controlled trial" with associated Boolean logic (and, or). Reference lists of all retrieved and relevant publications identified by these strategies were hand searched. The search was limited to English language publications. (See supplement 1 for full search strategy.)

2.3. Eligibility criteria

2.3.1. Types of participants

The review included studies with any patient admitted to an intensive care unit (ICU) who underwent blood sampling by any method. There was no limit on patient age.

2.3.2. Types of interventions

Trials comparing any blood conservation practice or product, including point-of-care microanalysis, closed-loop arterial sampling, small-volume phlebotomy tubes, or bundled approaches were included.

2.3.3. Study selection

All RCTs and clustered randomised trials (CRTs) that evaluated the effectiveness of blood conservation strategies for their impact on total blood sampling volume and other clinical sequelae were eligible for inclusion in the review.

2.4. Types of outcome measures

Primary outcomes:

- Blood sampling volumes in millilitres (ml) expressed as either daily or accumulative loss, overall and by subgroup (discard, sample type, total)
- Haemoglobin (g/dl) change during ICU admission

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Secondary outcomes:

- Packed red blood cell (PRBC) transfusion (number/proportion of patients and/or frequency)
- Frequency of blood sampling
- Frequency of repeated tests due to inaccuracy
- Colonisation of AC tip and/or intraluminal fluid by colony count and microorganism
- Primary, and all-cause, blood stream infection
- ICU length of stay
- Mortality
- Cost

2.5. Data collection/extraction

Results of the database search were imported into reference management software (EndNote X9). Duplicates were identified and removed with the help of EndNote program. Paired authors independently assessed titles and abstracts identified by the outlined eligibility criteria (S.K., S.M., and A.U.). Full copies of relevant studies were reviewed and assessed further. A third independent reviewer (S.K. or A.U.) clarified any discrepancies arising at any stage between the two authors.

Paired authors (S.K., S.M., and A.U.) independently extracted data from all the included studies using a data extraction form designed for this review. The data extracted included the following items: author, study type, title, year, country, setting, characteristics of participants (e.g., age, sex, and diagnosis), intervention, length of follow-up, primary outcomes, secondary outcomes. If information was unclear or missing, an attempt was made to contact the corresponding study author for further clarification or data. Again, a third author (A.U.) was available to arbitrate any disparities.

2.6. Quality appraisal

The Cochrane Collaboration Risk of Bias assessment tool was used to assess methodological quality and bias.[31] This tool addresses seven domains, namely randomisation and sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and 'other issues'. The tool provides a judgement relating to a study's risk of bias, assigning 'low risk', 'high risk', or 'unclear' risk of bias to each study. Paired authors independently assessed risk of bias (S.K., S.M., and A.U.). A third independent reviewer (S.K. or A.U.) clarified any discrepancies arising.

2.7. Data synthesis

Clinical, methodological, and statistical heterogeneities were considered. A random effects model was used due to the anticipated clinical and/or statistical heterogeneity present in the studies. Summary statistics were extracted, and data were pooled to measure treatment effect using the Mantel Haenszel (MaHa) model for meta-analysis of both dichotomous and continuous variables in RevMan 5.3, as appropriate, with results expressed as risk ratio (RR) (including 95% confidence intervals [CIs]), and statistical heterogeneity using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test. Sensitivity analyses and subgroup analyses based on study weighting or patient age were to be conducted if warranted. Meta-analysis was considered possible if two or more studies reported outcome data in the same format on the same variable for the intervention. Where meta-analysis was not able to be undertaken, due to poor study quality or heterogeneity, the review was limited to a narrative description of the results.

2.8. Reporting bias and certainty of findings

Assessment of publication bias and certainty was not conducted due to the small number of studies (i.e., less than 10 studies) and limited meta-analysis. Specifically, that meta-analysis was not possible for the primary outcomes.

3. Results

Six hundred and two studies were identified from databases and initial search. After duplicates were removed, 537 titles and abstracts were screened for inclusion. Nine studies were provisionally eligible for inclusion. One study was removed after full-text screening because of ineligible outcome measures.[32] A total of eight studies were eligible for data extraction and quality assessment.[5,24,33–38] See Fig. 1.

3.1. Characteristics

In total, the eight included studies evaluated outcomes on 1027 patients, with sample sizes ranging from 39 to 248 participants. All studies were conducted in ICU settings with six studies in adult populations,[5,24,33–35,37] one study in the paediatric population,[36] and one study in the preterm infant population.[38] Studies were conducted in a range of countries: two in Australia[5,33] and one each from Brazil,[35] China,[36] Ireland,[34] Japan,[24] the United Kingdom,[37] and the United States of America.[38] All studies used an RCT design. All studies were independently funded, with partial industry support of one study with equipment.[34] Six of the eight studies compared the standard open arterial blood sampling system to some form of a closed-loop arterial blood sampling system,[24,33,35–38] plus one study adding small-volume tubes to the closed-loop system.[34] The remaining study evaluated the impact of a conservative phlebotomy protocol alone, centred on use of small-volume sampling syringes and tubes compared to standard large-volume syringes and tubes.[5] Only four studies evaluated the impact of the intervention on blood sampling outcomes.[5,33,34,38] Other outcomes of interest centred on changes in haemoglobin (Hb; g/L or mg/dL) and the number of transfusions per ICU day or admission. Infection outcomes measured included local AC tip and administration set fluid colonisation as well as isolated microorganism. One study each reported data on catheter related infection[36] and mortality.[37] See Table 1 for characteristics of included studies.

3.2. Quality appraisal

Quality appraisal demonstrated generally a high risk of bias across the reviewed studies. Only two studies reported using a computerised randomisation system. In other studies, the randomisation method was either not stated or used opaque sealed envelopes. Similarly, allocation concealment methods were not stated and unclear for all studies. The nature of the intervention prevented blinding of participants or study personnel in all studies; however, in some studies, the outcome assessor was blinded. Overall poor reporting was observed, and no studies followed the Consolidated Standards of Reporting Trials (CONSORT) statement[39] which introduced potential bias in outcome reporting at different levels. See Figs. 2 and 3 for summary of risk of bias assessment.

Results are presented under each outcome. Data from studies that evaluated common interventions and/or studied common outcomes were pooled for meta-analysis, where possible.

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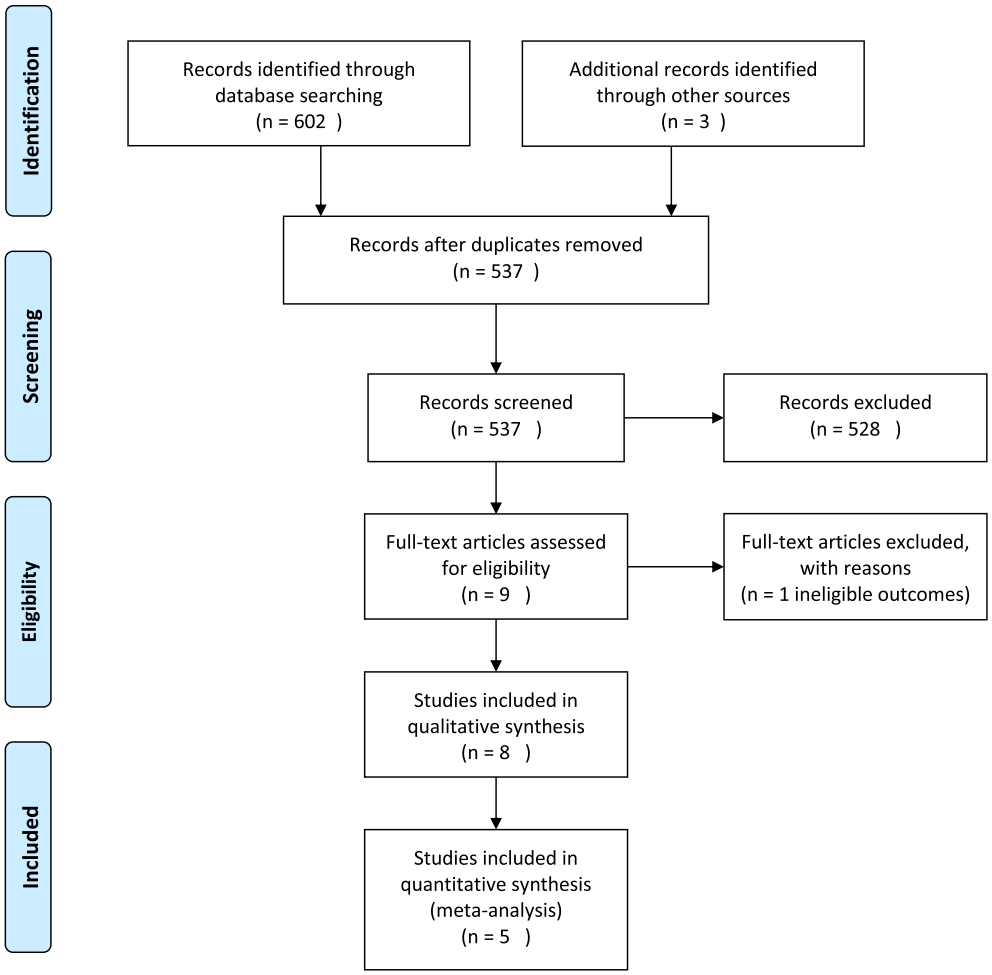

Fig. 1. PRISMA flow diagram of study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

3.2.1. Blood sampling volumes

Four studies evaluated the impact of blood conservation strategy(ies) on blood sampling outcomes.[5,33,38] These could not be pooled for meta-analysis because of significant clinical heterogeneity and reported statistics (i.e., medians as opposed to means). Both blood conservation interventions by Mahdy et al. and MacIsaac et al. were a closed-loop sampling system.[33,34] The intervention of Widness et al. was a type of closed-loop system with auto sampling and analysis.[38]

In the trial of Mahdy et al., the (closed loop) intervention resulted in mean total blood sample volumes being reduced from 45.11 ml (standard deviation [SD]: 14.05) control to 15.16 ml (SD: 5.32) in the closed-loop intervention arm ($p = 0.01$). This was largely attributed to reduction in discard volumes (from mean 24.83 [SD: 9.16] in the control arm to 0 ml in the closed-loop intervention arm [$p < 0.0001$]).[34] MacIsaac et al. also reported a reduction in total blood volume drawn over ICU admission related to the closed-loop blood sampling system (median and range in ml, control: 133 [7–1227] versus closed-loop intervention: 63 [0–787], $p = 0.03$).[33] Widness et al. modelled cumulative phlebotomy loss data and demonstrated significant differences between the two study groups throughout the entire study period, with the (closed loop and automated sampling) intervention group having 27% ($p = 0.04$) and 24% ($p = 0.46$) lower cumulative phlebotomy losses at weeks 1 and 2, respectively. Absolute blood sample loss volumes were not reported.[38]

The blood conservation intervention of Harber et al. consisted of return of line clearance volume and use of small-volume sampling syringes and tubes compared to a standardised but less conservative blood sampling protocol.[5] Their intervention arm demonstrated a reduction in median daily phlebotomy blood levels (PBLs) decreased from 40 ml (28–43) in the control arm to 8 ml (7–10) in the experiment arm ($p < 0.001$). Total median accumulative PBL for ICU admission also showed commensurate reduction from 141 ml (80–202) to 25 ml (14–33) in the experiment arm ($p < 0.001$).[5]

3.2.2. Hb change

Five studies measured changes in Hb levels over the ICU admission.[5,33–35,37] However, none of these could be pooled because of differing time scales, use of median values for Hb, or inadequate data reported (i.e., baseline and subsequent values reported but actual changes over time not and unable to compute due to lack of raw data). Regardless of scale or intervention (closed loop or conservative phlebotomy), no study reported a significant change in Hb between arms.

3.3. Secondary outcomes

3.3.1. PRBC transfusion use

Four studies measured the impact of the intervention on blood transfusion outcomes: the proportion of patients receiving transfusion,[33,35] the number of units,[37] or volume of PRBC

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Table 1
Characteristics of included studies.

First author (year) ref	Country	Setting	Sample size	Intervention	Primary outcome	Additional outcomes
Haber (2006)[5]	Australia	Adult ICU	N = 49 I = 24; C = 25	Conservative phlebotomy	Phlebotomy blood loss (PBL) Median (range) daily PBL I: 8 ml (7–10) vs C: 40 ml (28–43), $p < 0.001$ Median (range) total PBL I: 25 ml (14–33) vs C: 141 ml (80–202), $p < 0.001$	Mean difference Haemoglobin (Hb) change I: 1.3 g/dl vs C: 2.0 g/dl Number of blood transfusions I: 2/24 vs C: 3/25
MacIssac (2003)[33]	Australia	Adult ICU	N = 160 I = 80; C = 80	Closed-loop sampling system	Median (range) change in Hb during ICU g/l I: −7 (−84 to +21) vs C: −4 (−67 to +40), $p = 0.33$	N (%) patients transfused I: 17 (21) vs C: 30 (38), $p = 0.04$ Median (range) total blood drained over ICU stay I: 63 (0–787) vs C: 133 (7–1227), $p < 0.001$ Median (range) discard volume drawn per ICU day: I: 0.2 range (0–53) vs C: 21 (5–58), $p < 0.001$
Mahdy (2009)[34]	Ireland	Adult ICU	N = 39 I = 20; C = 19	Closed-loop sampling system and small-volume sampling tubes	Mean (SD) total blood drained I: 15.15 ml (5.32) vs C: 45.11 ml (14.05), $p < 0.001$	Mean (SD) blood discarded I: 0 ml (0) vs 24.83 ml (9.16) $p < 0.001$ Mean (SD) fall in Hb after 3 days I: 0.79 g/dl (0.61) vs C: 1.30 g/dl (1.13), $p = 0.09$
Oto (2012)[24]	Japan	Adult ICU	N = 211 I = 106 Pts; C = 105 Pts, I = 109 ACs; C = 107 ACs	Closed-loop sampling system	Catheter tip colonisation N (%) I: 8 (7.3) vs C: 11 (10.3), $p = 0.48$ per 1000 catheter days (95% CI) I: 12 (4–20) vs C: 22 (9–34), $p = 0.14$	Colonisation of intraluminal fluid N (%) I: 2 (1.8) vs C: 9 (8.4), $p = 0.03$ per 1000 catheter days (95% CI) I: 3 (0–7) vs C: 18 (6–29), $p = 0.02$
Rezende (2010)[35]	Brazil	Adult ICU	N = 127 I = 62; C = 65	Closed-loop sampling system	Mean difference Hb during ICU stay I: 0.7 mg/dl vs C: 1.5 mg/dl I: Mean (SD) baseline Hb mg/dl: 10.4 (2.37) and final Hb mg/dl 9.7 (1.3), $p = 0.012$ C: Mean (SD) baseline Hb mg/dl 10.5 (2.24) and final Hb 9.1 (1.80), $p = 0.002$	Proportion of patients receiving transfusion I: 30% vs C: 42%, $p = 0.158$ Mean (SD) daily transfused units I: 1.67 (1.05) vs C: 1.30 (0.46), $p = 0.26$ Mean (SD) total transfused units I: 2.25 (1.24) vs C: 2.52 (1.43), $p = 0.62$
Tang (2014)[36]	China	Paediatric ICU	N = 248 I = 128; C = 120	Closed-loop sampling system	Catheter tip colonisation N (%) I: 9 (6.1) vs C: 12 (8.8) $p = 0.40$ per 1000 catheter days (95% CI) I: 10 (5–15) vs 14 (8–20), $p = 0.30$	Colonisation of intraluminal fluid N (%) I: 3 (2.0) vs C: 10 (7.3), p = 0.03 per 1000 catheter days (95% CI) I: 3 (0–6) vs C: 12 (6–17), $p = 0.02$ Catheter-related blood stream infection (CRBSI) N (%) I: 0 (0) vs C: 2 (1.5), $p = 0.21$ per 1000 catheter days (95% CI) I: 0 (0-0) vs C: 2 (0–4), $p = 0.21$
Thorpe (2000)[37]	UK	Adult ICU	N = 100 I = 48; C = 50	Closed loop sampling system	Median (range) number of units transfused I: 2 (0–19) vs C: 2 (0–34)	Median (range) transfusion days I: 1 (0–7) vs C: 1 (0–16) Mean (SD) Hb levels at 7 days I: 11.2 (1.0) vs C: 11.1 (1.0) Positive blood culture N (%) I: 5 (10.4) vs C: 8 (15.3) Catheter tip colonisation N (%) I: 29/96 (30.2) vs C: 37/99 (37.3) Mortality N (%) I: 12 (25.0) vs C: 16 (30.7)
Widness (2005)[38]	USA	Neonatal ICU	N = 93 I = 42; C = 41		Mean (SD) cumulative transfusion volume (ml/kg) I: 38 (±3) vs C: 46 (±4), $p = 0.46$	Cumulative laboratory blood loss 27% and 24% lower in intervention group at weeks 1 and 2, respectively (absolute values not reported)

95% CI, 95% confidence interval; AC, arterial catheter; C, control; I, intervention; ICU, intensive care unit; N, sample size; Pts, patients; SD, standard deviation.

transfusion.[38] The intervention employed in all these studies was a closed-loop system. Two of these studies were amenable to meta-analysis.[33,35] Meta-analysis of data from two studies showed a significant difference between arms favouring the intervention (RR: 0.65 [95% CI: 0.46,0.92] $I^2 = 0$). See Fig. 4. Median units of blood transfused in the study by Thorpe et al. were equivalent between groups.[37] Data from the first week of the study by Widness et al. demonstrated a clinically significant 33% reduction in cumulative PRBC transfusion volume in the monitor group (22 ± 3 vs 33 ± 3 ml/kg; $p = 0.04$). However, over the full 2-week study period, the difference in PRBC transfusion volume was moderate and nonsignificant, with a 17% reduction in cumulative PRBC transfusion volume per infant in the monitor group versus the control group (38 ± 3 vs 46 ± 4 ml/kg; $p = 0.46$), when these data were adjusted for study site and duration of umbilical arterial catheter (UAC) use.[38]

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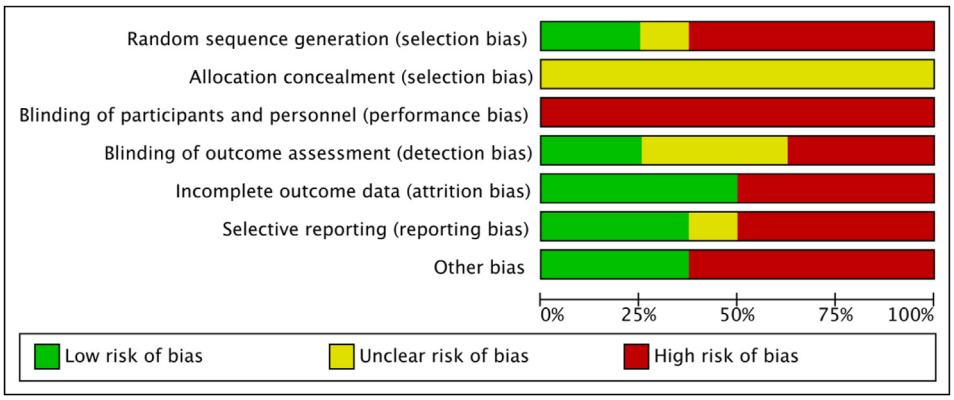

Fig. 2. Risk of bias graph.

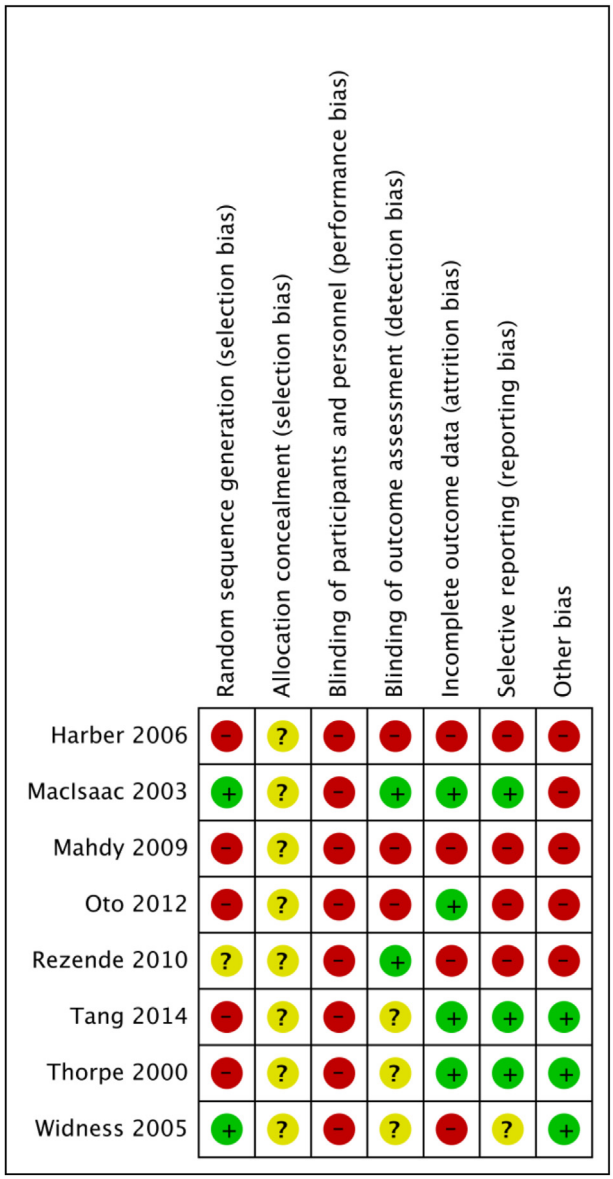

Fig. 3. Risk of bias summary.

3.3.2. Number of blood tests

One study measured and reported on changes in frequency of actual tests. Harber et al. stated that the absolute number of tests per patient was not statistically different ($p = 0.42$) between their standard care and conservative phlebotomy groups, but the actual data were not reported.[5]

3.3.3. Colonisation

Three studies measured level of colonisation.[24,36,37] AC tip colonisation in all three showed no evidence of difference between closed-loop intervention and control groups (RR: 0.78 [95% CI: 0.56, 1.08], $I^2 = 0$). Intraluminal fluid colonisation measured in two studies (see Fig. 5) was significantly reduced for closed-loop systems, in comparison to open systems (RR: 0.25 [95% CI: 0.07, 0.58], $I^2 = 0$).[24,36] Coagulase-negative *staphylococci* was the most commonly detected microorganism across all three studies.

3.3.4. Infection

Three studies stated that they measured infection or adverse events, though definitions were nondescript and varied. No meta-analysis was possible. Only one study referred specifically to CRBSI. Tang et al. reported low and comparable incidence and rates between arms (control 2/137 [1.5%] or 2/1000 catheter days [95% CI: 0, 4] versus 0 cases in the closed-loop intervention arm, $p = 0.21$).[36] Thorpe et al. reported no catheter-related sepsis in either the closed-loop intervention or control arms.[37] MacIsaac et al. stated that there were no adverse events detected in either the closed-loop intervention or control arm during the trial.[33]

3.3.5. Mortality

Overall, mortality was poorly reported across reviewed studies. The study by Thorpe et al. was the sole study to report incidence of mortality (reported as *survivors to ICU discharge*). Incidence of mortality was higher in the control arm (16/52 [31%]) than in the intervention arm (12/48 [25%]).[37] The reason for this was not explored in the study. Mean APACHE II scores were comparable between groups (control: 19 [±7] versus closed-loop intervention: 18 [±8]), indicating comparable severity of illness. Harber et al. stated that mortality was not significantly different in the conservative phlebotomy or control groups; however, no figures were reported.[5] MacIsaac et al. stated there were no study-related adverse events in either the closed-loop intervention or control arm.[33]

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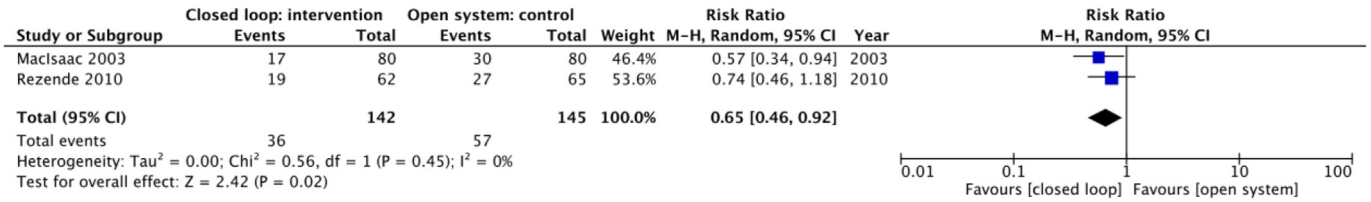

Fig. 4. Forest plot of closed-loop versus open system sampling on proportion of patients receiving transfusion. CI, confidence interval.

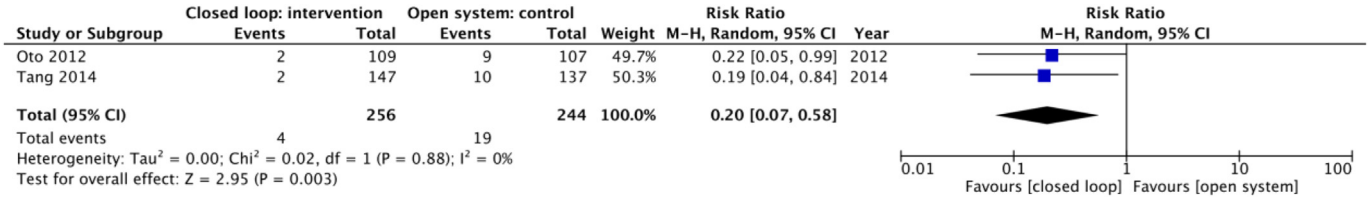

Fig. 5. Forest plot of closed-loop versus open system sampling on intraluminal fluid colonisation. CI, confidence interval.

3.3.6. *ICU length of stay and severity of illness*

Three studies measured ICU length of stay.[5,33,35] Severity of illness as reflected in APACHE II scores was measured in five studies.[5,24,33,36,37] These variables were measured and reported as patient characteristics to describe and summarise the sample and demonstrate equivalence at baseline between study groups rather than as outcome variables. They were not amenable to meta-analysis.

3.3.7. *Cost*

No studies reported on the impact of blood conservation strategies on costs.

4. Discussion

Diagnostic blood sampling is vital to inform ICU decision-making management; however, our practices should not result in harm. The aim of this review was to evaluate the impact of different blood sampling strategies and systems in intensive care on blood sampling outcomes and other sequelae. Most studies (7/8) evaluated the impact of a closed-loop sampling system. Meta-analysis was not possible due to heterogeneity of reporting for many planned outcomes. However, where possible, meta-analysis demonstrated that closed-loop systems significantly reduced the need for transfused blood (RR: 0.65) and intraluminal colonisation (RR: 0.20), with clinically important effect sizes. Reducing the need for blood transfusion, the risk of CRBSI and related morbidity and mortality are an important focus of critical care practice.

Individual results from three studies demonstrated that closed-loop systems were associated with reduced blood sampling volumes.[33,34,38] A fourth study reported reduced sample losses related to use of small-volume blood sampling tubes.[5] Significant changes in Hb were not observed. Likewise, significant differences in bloodstream infection, length of stay, and mortality were not reported. However, the overall quality of measurement and reporting of these variables was poor, and there were insufficient data to make firm conclusions about the impact of interventions on key outcomes. These results concur with previous reviews exploring similar question across older and nonrandomised studies.[27,28] Notably, now new randomised trials were identified after 2014. However, observational studies have demonstrated reduction in blood sampling volumes, transfusion use, and ICU length of stay associated with implementation of blood conservation practice and strategies.[40,41]

The costs of implementing alternate sampling systems or strategies are unknown. None of the included studies measured and reported this. New arterial sampling systems may be associated with increased acquisition or training costs. However, this needs to be weighed against the cost of treating iatrogenic anaemia and infection though transfusions, antibiotics, and extended ICU stay.

Blood collection is a vital part of intensive care to help in decision-making. Vascular access devices linked to fluid administration and monitoring systems help with this. The presence of arterial or central venous catheters has been associated with increased sampling blood losses.[2,11] Further, the amount of overdraw volumes from arterial lines were higher when sampling from vascular access devices.[42] So, although these devices facilitate more efficient medical care in the ICU, there is an onus on clinicians to use the devices and test judiciously and responsibly. Unnecessary laboratory testing is common in the ICU,[1,43] but to modify test-ordering and blood sampling practices in the ICU is challenging. It is challenging to know which tests are absolutely necessary in the interdisciplinary and dynamic ICU environment. However, it has been reported that up to 48% of laboratory tests performed routinely in the ICU have normal results.[44] The risk of compromising patient care as a result of underinvestigation has to be balanced against wasteful overinvestigation. Getting the balance right is difficult.[45] To minimise blood sample loss and reduce risk of CRBSI in the ICU, multimodality blood conservation strategies inclusive of behavioural modifications to ensure minimum test ordering, small-volume collection tubes, contemporary point-of-care testing, and use of closed systems to reduce device contamination are indicated.

4.1. *Limitations of review*

This study has some important limitations. These are primarily related to the small number of studies eligible for review, as well as the heterogeneity of reported outcomes. As such, it was not possible to pool results of all outcomes between studies. A high risk of bias was identified in selected studies largely related to randomisation technique and lack of blinding and also incomplete outcomes and selective reporting. Additionally, the sample sizes of included studies were small (median: 127, range: 39–248). Further, despite date limiters on the database search, many of these studies are now relatively dated with no new studies conducted since 2014. Therefore, included studies are likely not reflective of current ICU practice. Results are suggestive of the effectiveness of interventions such as closed-loop systems and conservative phlebotomy on

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reducing blood sample losses and infection risk, and firm conclusions cannot be drawn.

5. Conclusions and recommendations

Closed-loop sampling systems are associated with reduced PRBC blood transfusions and reduced colonisation of intraluminal fluid. Findings from individual studies employing different conservation strategies also indicate possible reduction in blood sample losses. However, risk of bias, heterogeneity of intervention, and variability in outcomes reported in the primary studies limit conclusions of this review. Managing blood sampling for critically patients is a complex behavioural and procedural process. It is likely a systems approach encompassing a bundle of strategies would produce the most effective and sustainable impact of clinical practice. Confirmation of impact of blood conservation practices and implementation strategies in larger, contemporary, rigorous effectiveness-implementation trial analysis using clinically relevant outcomes is required.

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CRediT authorship contribution statement

Samantha Keogh: Conceptualisation, Methodology, Funding acquisition, Data curation, Formal analysis, Validation, Writing - original draft, Writing – reviewing & editing. **Saira Mathew**: Methodology, Data curation, Formal analysis, Validation, Writing – reviewing & editing. **Amanda Ullman**: Conceptualisation, Methodology, Funding acquisition, Data curation, Formal analysis, Validation, Writing – reviewing & editing. **Claire Rickard**: Conceptualisation, Validation, Writing – reviewing & editing. **Fiona Coyer**: Conceptualisation, Funding acquisition, Validation, Writing – reviewing & editing.

Conflict of interest

S.K. reports monies received by her employer QUT from BD Medical and ITL Biomedical for educational consultancies received not related to this study.

A.U. reports research funding received by her employer (Griffith University) for investigator-initiated research grants from product manufacturers (3M, Becton Dickinson, Cardinal Health) unrelated to the current study.

C.R. reports research funding received by current or previous employers (University of Queensland and Griffith University) for investigator-initiated research grants or consultancies from product manufacturers (3M, Becton Dickinson, Cardinal Health, Eloquest) unrelated to the current study. S.M. and F.C. have no disclosures to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aucc.2022.12.002.

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