Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis
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CRD summary
This review concluded that restrictive red blood cell transfusion strategies, compared with liberal strategies, could reduce the risk of serious health care-associated infection. This was a generally well-conducted review, but the finding for serious infections was only just statistically significant, so the authors' conclusions seem overly strong and should be considered alongside the harms associated with each strategy.

Authors' objectives
To assess whether red blood transfusion strategy thresholds are associated with a risk of infection and whether risk persists in patients who receive leukocyte-reduced red blood cells.

Searching
Eight electronic sources were searched to January 2014 with no restrictions on language and publication status. Search terms were reported.

Study selection
Eligible studies were randomised controlled trials (RCTs) that compared the effects of a restrictive versus a liberal red blood cell transfusion strategy on infectious outcomes. There were no restrictions on patient age or medical condition.

Included trials were published between 1995 and 2014 and conducted in one or more countries including USA, Canada, Europe (three in UK), Brazil and Australia. Trials were in patients with cardiac or orthopaedic conditions, critical illness, gastrointestinal bleeding, low birth weight, sepsis or sickle cell anaemia and in postpartum women. One trial included infants with a mean gestational age of 26.1 weeks. Where reported, patients in the other trials ranged from 7.3 months to 83.3 years of age. Baseline haemoglobin levels were similar across treatment groups. Haemoglobin transfusion thresholds in trials of adults ranged from 6.4 to 9.7 g/dL in the restrictive groups and from 9.0 to 12.0 g/dL in liberal groups. Infection outcome definitions varied across trials.

Two reviewers independently screened studies for inclusion; discrepancies were resolved through consensus.

Assessment of study quality
Two reviewers extracted data on quality criteria for randomisation concealment, blinding, loss to follow-up and protocol violations. Any discrepancies between reviewers were resolved through consensus.

Data extraction
Cumulative risks of infection in both treatment groups were extracted to calculate risk ratios and 95% confidence intervals for each trial. Where hazard ratios were reported, these were used to approximate risk ratios. The number needed to treat for each trial was calculated.

Two reviewers independently extracted outcome data; any discrepancies were resolved through consensus.

Methods of synthesis
A DerSimonian and Laird random-effects model was used to combine risk ratios for all serious infections and separately by infection type. Variance was stabilised using the enhanced Freeman-Tukey arcsine transformation. Statistical heterogeneity was assessed using $I^2$, Cochran's Q test and the $I^2$ statistic.

Sensitivity analyses were performed by excluding a study that reported results as hazard ratios and based on quality criteria. Results were also stratified by clinical setting and by patients who used leukocyte-reduced red blood cells and unknown or partial use of leukocyte-reduced red blood cells.

Meta-regression was conducted to assess the effects of different haemoglobin thresholds in liberal and restrictive
treatment groups on risk ratios.

Publication bias was assessed through visual inspection of funnel plots and using the Harbord test of small study effects and Peters test of funnel asymmetry.

**Results of the review**
[Data corrected 22.12.14]

Twenty trials (8,598 participants, range 45 to 2,016) were included in the review. Fifteen trials reported concealment of randomisation and 10 trials reported blinding in patients, surgical staff, outcome assessors or investigators. Withdrawals ranged from none to 17%. Where protocol violations occurred, these were generally below 10%; one trial reported non-adherence to protocol in 59% of liberal patients and 16% of restrictive patients.

Where reported, transfusions were used in 13% to 89% of patients in the restrictive groups and in 31% to 100% of patients in the liberal groups.

Seventeen trials (7,456 patients) were included in meta-analysis. There was a reduction in infections using restrictive thresholds, compared with liberal strategies, but this was not statistically significant. For serious infections, the reduction was just statistically significant (RR 0.84, 95% CI 0.73 to 0.96; eight RCTs). For every 1,000 patients in which red blood cell transfusion was considered, 21 could be spared any infection if restrictive strategies were used, and 48 spared a serious infection. The authors did not report the number needed to treat for liberal strategies.

Stratification by clinical setting showed that the association between restrictive versus liberal thresholds favoured restrictive transfusion in orthopaedic patients (RR 0.72, 95% CI 0.53 to 0.97; four RCTs) and children with sepsis (RR 0.51, 95% CI 0.28 to 0.95; one RCT). Findings in other clinical settings were not statistically significant.

There was no evidence of significant statistical heterogeneity. Other findings were reported in the review. There was no evidence of publication bias.

**Authors’ conclusions**
Restrictive red blood cell transfusions, compared with a liberal transfusion strategy, could reduce the risk of serious health care-associated infection.

**CRD commentary**
The review question and inclusion criteria were broadly stated. Several sources were searched for relevant literature and there were no language and publication restrictions (which minimised potential for missed data). Trial quality was assessed and was taken into consideration in the evidence synthesis. Each stage of the review process was performed in duplicate (which reduced potential for reviewer error and bias).

The evidence base was large. Appropriate methods were used to combine outcome data. Forest plots revealed wide confidence intervals for most individual trials. There was no evidence of significant statistical heterogeneity but the authors acknowledged clinical heterogeneity between trials in terms of groups of patients, infectious definitions and haemoglobin thresholds.

This was a generally well-conducted review and the evidence base was large. The main findings were only just statistically significant so the authors’ conclusions seem overly strong and should be considered bearing in mind other harms associated with the different strategies.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further trials may provide insight into the risks and benefits of the two transfusion strategies. Future trials should uniformly measure health care-associated infection as defined by the US Centres for Disease Control and Prevention.

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