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TITLE: Red cell transfusions: is less always best?

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CONFLICTS OF INTEREST: AM, SS, JS, EW and ZM are authors of papers discussed in this article, and are also investigators on the REDDS-2 trial which is discussed in this article. SS, EW and ZM were investigators on the REDDS trial which is also discussed in this article.

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RUNNING HEADLINE: *RBC transfusions: is less always best?*

ABSTRACT: Restrictive transfusion strategies are now largely regarded as standard of care in many clinical settings, but is this truly optimal care for all patients? This commentary critically reviews the evidence behind restrictive red cell transfusion strategies and explores the question of whether this is appropriate in all patient groups. In particular, issues surrounding the limitations of trial data in certain settings (such as patients with cardiac disease, hematologic malignancies and chronically transfused outpatients) are highlighted as we explore whether less may not always be best. Methodological challenges in transfusion trials and whether the correct outcome measures are being measured are also discussed.

KEY WORDS: Restrictive transfusion, liberal transfusion, patient blood management

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"Red cell transfusions: is less always best?"

How confident are we that restrictive transfusion strategies should be the standard of care default transfusion practice?

The rationale for restrictive transfusion policies in patient blood management and 70g/L as the default hemoglobin threshold for red cell transfusion

Patient blood management (PBM) is defined by the International Society of Blood Transfusion (ISBT) as "an evidence-based, multidisciplinary approach aimed at optimising the care of patients who might need transfusion… [putting] the patient at the heart of decisions made around blood transfusion, promoting appropriate use of blood and blood components...".[1] The goal of PBM is ultimately to improve patient care and optimise patient outcomes in relation to transfusion practice. Many PBM guidelines promote the use of restrictive transfusion strategies in various clinical settings (in particular, surgery and critical care),[2,3] with the goal of reducing avoidable transfusions and their associated risks. Whereas previously common medical practice was to use higher hemoglobin (Hb) transfusion triggers for red blood cell (RBC) transfusion approaching 100g/L, clinical trials from the late 1990s onwards in acute and critical care settings showed that lower thresholds for patients in these settings did not cause harm; for example, the pivotal Transfusion Requirements in Critical Care (TRICC) trial showed no difference in 30-day mortality, with possible superiority of the restrictive strategy in certain subgroups (patients who were less acutely ill and patients under 55 years of age).[4] Recommendations arose to adopt a RBC transfusion threshold of 70g/L as the standard of care in most clinical situations.[5]

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This was further supported by a 2016 Cochrane review of 31 randomized trials with a total of 12,587 patients,[6] subsequently updated in 2018.[7] This review found that transfusing RBCs at a restrictive threshold of Hb 70g/L to 80g/L, compared to a liberal Hb threshold of 90g/L to 100g/L, did not adversely affect 30-day mortality, or any other adverse outcomes which were measured (such as thromboembolism, stroke, cardiac events).[6] Consequently, management strategies such as using restrictive Hb thresholds (typically <70g/L or 80g/L) have been widely adopted into clinical practice for hemodynamically stable general medical[8] and surgical[2] patients. Further, RBC usage or transfusion rates, as surrogate markers of a successful 'restrictive' transfusion strategy program, are often now used as a key quality performance outcome indicator by governments and health services.[9]

At one level, these recommendations based on a large number of randomized trials seem very firm. However, closer inspection of the trials reveals a number of challenges, which limits the strength of interpretation of these findings. In this commentary, we address these issues and limitations, to explore the question of whether *less may not always be best*.

Limitations of the evidence base supporting restrictive transfusion recommendations

The authors of the Cochrane review[6] and its 2018 update[7] highlight a number of limitations. These include whether the findings are necessarily generalizable to all patient subgroups, the lack of trials in outpatients and the importance of outcomes other than mortality.

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In addition, a number of methodological problems have been described, including potential bias due to lack of blinding, the relevance of arbitrarily selected Hb concentrations defining restrictive versus liberal transfusion arms, the lack of a "usual care treatment group" as comparator[10] and the heterogeneity of patients. These problems are apparent in the recommendations of the 2018 Frankfurt Consensus Conference in PBM, which highlighted the low-quality evidence available in many settings, including in many patients who currently receive long-term transfusion support.[11]

These potential limitations will now be discussed in turn.

Restrictive transfusion strategies may not apply to all clinical subgroups

A large body of evidence supports the overall safety of a restrictive transfusion strategy in many clinical settings. Although the 2016 Cochrane review showed no difference in 30-day mortality for restrictive versus liberal transfusion strategies,[6] clinical equipoise still remains for various patient subgroups, due to the patient populations included in the trials conducted to date. The majority of the 31 included trials[6] were in surgical, critical care or trauma settings. The authors highlighted a paucity of robust clinical data in certain clinical subgroups where patients are frequently transfused, including acute coronary syndrome or acute myocardial infarction (AMI; only two included trials), neurological disorders, thrombocytopenia, cancer, hematological malignancies (only two trials, both in acute leukemia), bone marrow failure and in patients receiving intensive chemotherapy or radiotherapy. More recent pilot trials in these groups also raise questions about potential harm with restrictive thresholds. A pilot trial in patients undergoing vascular surgery

showed higher rates of death or vascular complications for patients transfused to a lower Hb trigger (<80g/L versus <97g/L).[12] Another pilot trial in patients with head trauma showed lower hospital mortality and improved neurological recovery favoring the liberal group.[13]

Different patient subgroups are likely to have different pathophysiological responses to anemia and transfusion. This is reflected in differences in outcomes for two subgroups in the Cochrane review: those with gastrointestinal (GI) bleeding (including acute GI bleeding and trauma-related bleeding) compared with patients with AMI. These were the only subgroups in which there was a difference in 30-day mortality for restrictive versus liberal transfusion thresholds. In the GI bleed subgroup (1522 patients in three trials), a restrictive strategy was associated with a 25% lower 30-day mortality, possibly due to a lower rebleeding risk. The authors postulated this may be related to higher vascular pressures following transfusion in the liberal group. Contrastingly, in patients with AMI (154 patients in 2 trials), the restrictive group had a higher 30-day mortality (albeit with a wide 95% CI of 0.83-18.31).[6]

Evidence and questions in patients with cardiac disease

In patients with underlying cardiac disease, the pathophysiology and physiological response to anemia may be very different to patients with acute anemia due to trauma or bleeding. Anemia results in a compensatory increase in cardiac output. Chronic severe anemia, however, may lead to long-term left ventricular dysfunction and remodelling due to peripheral vasodilation with hypotension, and increased neurohormones (catecholamines, natriuretic peptides, renin-angiotensin-aldosterone and vasopressin) resulting in increased

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plasma volume and cardiac workload.[14] Patients with underlying cardiovascular disease have low reserve and limited abilities to deliver oxygen to tissues during anemia or critical illness. Myocardial oxygen delivery is further impaired by atheromatous disease.[14] One quarter of ICU patients with underlying cardiovascular disease experience AMI, the majority of which are due to oxygen supply-demand imbalance.[15] Furthermore, in patients with myelodysplastic syndromes (MDS), many of whom are elderly and require regular transfusion support, anemia itself is an independent predictor of poorer cardiovascular outcomes such as cardiac failure, coronary artery disease, cardiac remodelling, cardiac arrhythmia and overall cardiovascular mortality.[16] This is in contrast to acute trauma or bleeding-related anemia in otherwise fit patients with adequate cardiac reserve to appropriately compensate to lower Hb levels in the short-term.

Patients with cardiovascular disease represent a large proportion of transfusion recipients. There have been a number of trials specific to this patient group.[17-23] The updated 2018 Cochrane review focusing on this patient group identified trials enrolling 8645 patients undergoing cardiac surgery and 8898 patients with cardiovascular disease.[7] This review found that in patients undergoing cardiac surgery, a restrictive transfusion strategy was safe, with no difference in survival or other important clinical outcomes, compared to a liberal strategy.[7] Since then, updated Transfusion Requirements in Cardiac Surgery (TRICS) III trial data have also been published, which showed no difference in six-month outcomes for the composite outcome of death, AMI, stroke or new-onset renal failure with a restrictive versus liberal strategy in 5243 patients undergoing cardiac surgery.[17]

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However, as previously described, there is insufficient evidence in patients with AMI.The two small included trials (154 patients in total) in the Cochrane review showed a mortality risk ratio of 3.88, albeit with a wide confidence interval (95% CI 0.83-18.13), favoring the liberal transfusion group.[7] This included the Myocardial Ischaemia and Transfusion (MINT) pilot trial showing higher 30-day mortality in the restrictive group, in 110 anemic patients with acute coronary syndrome or stable angina undergoing cardiac catherization.[18] A separate systematic review and meta-analysis in patients with cardiovascular disease in a non-cardiac surgery setting, which included 11 trials enrolling 3033 patients, found a higher risk of acute coronary syndrome in patients managed with restrictive versus liberal transfusion strategies (RR 1.78; 95% CI 1.18 - 2.7).[24] In all, these equivocal findings demonstrate there is ongoing uncertainty in patients with AMI and that more data are needed in this area; the Phase 3 randomised MINT trial (3500 patients)[25] and the Restrictive and Liberal Transfusion Strategies in Patients with Acute Myocardial Infraction (REALITY) trial (630 patients)[26] are ongoing.

Evidence and remaining questions in patients with hematologic malignancies

Patients with hematologic malignancies are also poorly represented in clinical transfusion trials reported to date. Despite their high transfusion requirements, few trials have investigated restrictive versus liberal transfusion thresholds in patients undergoing intensive chemotherapy/ radiotherapy or hematopoietic stem cell transplantation (HSCT), as highlighted by a 2017 Cochrane review which identified only four studies involving such patients (240 patients). This demonstrated low-quality evidence of little or no effect on outcomes including 30- or 100-day mortality, bleeding or hospital stay.[27]

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Since then, the Study of Red Blood Cell Transfusion Triggers in Patients undergoing Hematopoietic Stem Cell Transplantation (TRIST trial) comparing Hb triggers of 70g/L versus 90g/L in 300 patients undergoing autologous or allogeneic HSCT found no significant differences in clinical outcomes or quality of life (QoL) scores between the two strategies.[28] This trial provides valuable information, as it is the largest trial to date to evaluate restrictive transfusion thresholds in hematology patients receiving intensive chemotherapy. However, limitations include patients and clinicians being non-blinded, which may affect QoL reporting (the primary outcome). Further, patients had a low comorbidity score overall; this likely reflects choosing 'fit' patients to receive HCST but may make the findings less applicable to a broader hematology patient population receiving chemotherapy, who may be older with comorbidities. The 2018 International Consensus Conference on PBM highlighted the low-quality evidence in the hematology and oncology setting and recommended further research in transfusion support in such patients.[11]

Evidence in chronically transfused patients in outpatient settings

As highlighted by the Cochrane review, there is a lack of trials in outpatient settings for chronically transfused patients.[6]

Chronically transfusion-dependent patients and/or those with concomitant bone marrow failure have different transfusion support requirements to those requiring transfusion in an acute setting. They also account for a large proportion of RBC transfusions, with a NHS Blood and Transplant (UK) audit showing that hematologic conditions (including

hematologic malignancies, bone marrow failure and hemoglobinopathies) accounted for 27% of total transfused RBC units[29] and an Australian audit similarly showed 33% of transfused RBCs were administered to hematology/oncology patients.[30]

Of all hematologic indications, patients with MDS receive the most RBC units.[29] The US REDS-III transfusion recipient database recorded 25,939 outpatient RBC transfusion encounters over 2 years (compared with 69,726 for inpatients), with the majority for blood disease (n=8206, 32%) or neoplasm (n=7013, 27%).[31] MDS are acquired bone marrow failure disorders, characterised by dysplasia and cytopenias. Over half of patients will require at least one RBC transfusion, and one-third are transfusion-dependent[32]. Patients with MDS are generally elderly, with median age 79 years and comorbid conditions are common, affecting 55% of patients.[32] In a US Medicare study, 73% of MDS patients had a cardiac event during a 3-year follow-up period, at significantly higher rates than the age-adjusted general population.[33] The 2016 Cochrane review included only two small feasibility trials in hematology patients, both in acute leukemia[6] and in an inpatient setting, which likely represents a different clinical scenario to chronically transfused elderly MDS outpatients.

Many PBM guidelines acknowledge the lack of evidence in MDS, and give no recommendation about Hb thresholds[8,34] in this setting, with recommendations only to transfuse to alleviate symptoms of anemia. Observational studies and practice surveys suggest that common practice is to use a restrictive transfusion strategy. In a recent national blood audit in the UK, 610/635 patients with MDS were transfused for anemia with a mean pre-transfusion Hb concentration 82.4g/L, SD 13.0.[35] The European MDS (EUMDS) registry found the most common threshold across Europe was 80g/L, although this varied

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between countries.[36] A recent Australian and New Zealand clinical practice survey indicated that the majority of clinicians use a restrictive approach in transfusion-dependent MDS patients (typically transfusing at Hb<80g/L, and aiming for a post-transfusion Hb 90-100g/L),[37] likely adapted from clinical trials and guidelines in acute settings. However, MDS patients with anemia have reduced overall survival – an observational study showed higher mortality in MDS patients with Hb concentration <80g/L in females and <90g/L in males, mostly due to cardiac-related deaths.[38]

However, it is currently unclear whether a higher Hb threshold in chronically transfused MDS patients would improve survival or QoL and, if so, what that Hb target should be. Several recently completed or ongoing studies aim to address this question. The recently published Red Cell Transfusion in Myelodysplastic Syndromes (REDDS) study[39] demonstrated feasibility of randomizing and maintaining blinding of 38 transfusion-dependent MDS patients randomized to a restrictive versus liberal transfusion threshold. A separation between the mean pre-transfusion Hb of 17g/L between the two arms was successfully achieved. In the similarly designed RBC-Enhance pilot study (recently reported in abstract form) which compared liberal versus restrictive transfusion strategies in MDS patients, a separation of mean Hb was also achieved between the two arms, although this did not meet the prerequisite feasibility endpoints.[40] Interestingly, in the REDDS study, patients in the liberal transfusion arm maintained a more stable pre-transfusion Hb, and also, in exploratory analyses, demonstrated better QoL scores than those in the restrictive arm.[39] These results appear to align with an observational study reporting lower amplitude of Hb change in MDS patients treated with either ESAs or transfusion therapy, was significantly correlated to improved QoL and less fatigue.[41] Some QoL signals also appeared

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to be improved in the liberal arm of the RBC-Enhance study.[40] However, these potential benefits in QoL and symptoms will need to be assessed against the risks of increased RBC usage (the liberal arm used approximately twice the number of RBC units versus the restrictive arm in the REDDS trial[39]) such as transfusion reactions, iron overload and cost, in future larger prospective clinical trials. The question of the benefits of maintaining a more stable Hb, by adopting a more frequent low-dose transfusion schedule, will be addressed prospectively in the REDDS-2 pilot study.[42] Ongoing studies in France (NTC 03643042)[43] are also investigating transfusion thresholds in MDS patients.

Conversely, transfusion thresholds lower than 70g/L may be appropriate in other patient populations such as sickle cell disease, in which the steady state Hb varies between different genotypes and even amongst different patients with the same genotype. Guidelines recommend considering the patient's steady state Hb, sickle Hb percentage and clinical condition, rather than transfusing to a specific Hb threshold, given the potential complications of transfusion in this cohort, including alloimmunisation, hyperviscosity and long-term iron overload.[44,45]

Such differences in diverse patient populations suggests that a 'one-size fits all' approach using prescribed restrictive transfusion thresholds may not be appropriate, and individualised patient approaches taking into consideration patient and disease characteristics, is needed.

The need for more clinical outcome measures in transfusion trials: quality of life, physical function and health economics

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Short- to medium-term mortality (for example, 30- or 100-day mortality) is commonly used as the primary outcome in clinical transfusion trials, with other common outcome measures including bleeding rates, infection, thromboembolic events, length of hospital stay and RBC usage. As the majority of these trials have been in acute, critical care or surgical settings, these are highly clinically relevant outcomes to those patient populations, and of significant interest to clinicians and health services.

However, as highlighted by the Cochrane review and others,[6,10] other outcomes may be more appropriate for different patient groups. For example, in elderly patients with MDS, in whom there are limited curative options, other outcomes such as maintaining or improving QoL and physical function are also important to address. MDS patients have been shown to have consistently worse QoL outcomes and symptoms than the general population.[46] Transfusion dependence is an independent predictor of impaired global health status[46] and anemia is associated with poorer QoL.[47] Treatment of anemia and improvement in Hb can subsequently improve QoL, as demonstrated by studies of erythropoiesis-stimulating agents (ESAs) in MDS.[48-50]

However, there are very few transfusion trials in MDS reporting QoL as a primary outcome. A systematic review of QoL and use of RBC transfusion in MDS identified only small studies with heterogeneous use of QoL instruments and poorly defined transfusion protocols.[51] It is currently difficult to compare QoL outcomes across different studies given the heterogeneity of instruments used and the differing timepoints when they are administered. Furthermore, commonly used QoL instruments in MDS trials include the EQ-

5D-5L, EORTC QLQ-C30 or FACT-Anemia[51]; however these are not specific to MDS and thus may not fully capture the impact of MDS-related treatments and symptoms. As such, newer disease-specific instruments such as the Quality of Life in Myelodysplasia Scale (QUALMS)[52] may be more relevant. Future trials should ideally consider using more disease-specific measurements, and at standardised timepoints to enable comparison across studies.

The effect of RBC transfusion on patients' physical function has also been poorly described . There is increasing interest in this area, from patients, clinicians and others. The recently published Red Cells in Outpatients Transfusion Outcomes Study from the National Heart, Lung, and Blood Institute REDS-III program[53] prospectively studied 208 patients receiving outpatient transfusion, and found that approximately 70% had improvements in their 6-minute-walk-test or fatigue scores (via the Functional Assessment of Chronic Illness Therapy scale). However, this study included patients with a wide range of benign hematology and hematology/oncology conditions, and was not restricted to MDS. Future studies could also consider sarcopenia assessment (low muscle mass and function), which is more common in the elderly and associated with impaired QoL, increased mortality and prolonged hospitalisations.[54,55] Sarcopenia, tested via handgrip strength using a hand dynamometer, has been associated with anemia, however the effect of transfusion is unclear.[56] There is also increasing interest in the use of wearable non-invasive accelerometers[57] to capture the effect of transfusion on daily physical activity.

Furthermore, although the end goal of RBC transfusion is to improve tissue and cellular oxygenation, very few trials have incorporated technologies to investigate this. A few studies have tested maximum exercise capacity and oxygen consumption (VO_2 max) using

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cycle ergometers with variable results in MDS patients treated with ESAs.[58,59] A transfusion trial in vascular surgery monitored intraoperative oxygen desaturation in the brain and muscle using near-infrared spectroscopy.[12] Given technical advances in non-invasive monitoring and the common use of wearable devices in the general community to monitor physiological signs, it is surprising that we still largely rely on a single biomarker (Hb) to guide transfusion therapy rather than incorporating such technologies in outpatients.

Other outcome measures which have been underutilized are qualitative outcomes. Although QoL surveys are useful, detailed information about patient experiences and preferences about their care may not be fully captured in a brief questionnaire. For example, the commonly used FACT-Anemia[60] survey assesses fatigue and other anemia-related symptoms in patients with cancer. However, the individual patient's wider experiences of transfusion treatment, including potential barriers, negative aspects, perceived benefits, and impacts on their overall psychosocial wellbeing and daily life are not well captured. Qualitative research methods may be valuable in future clinical trials to explore these issues in greater depth. Through in-depth interviews, focus groups or observations, these are able to explore complex social and behavioural phenomena not amenable to quantitative research, such as patients' private beliefs, experiences or behaviours.[61] Qualitative methods might be particularly valuable to explore areas with little prior knowledge, and to develop conceptual frameworks and engage stakeholders (such as patients and clinicians) around transfusion policy development.[62] For example, a qualitative study using semi-structured interviews explored the experiences of patients with hemophilia and von Willebrand's disease to identify challenges for such individuals and their families.[63] Clinician attitudes towards single RBC unit transfusion in the obstetric setting,

and internal/external factors influencing practice, were evaluated in another qualitative study.[64] Such research has the potential to result in policy changes to improve transfusion practice.

It is also imperative for future clinical trials to incorporate detailed health economics analyses, to adequately inform future health policy development in blood transfusion. The TITIRe2 trial in cardiac surgery reported no significant difference in total costs between the liberal versus restrictive threshold groups, taking into account costs of blood products, length of hospital stay, resources associated with complications and other patient care up to three months post-surgery.[23] The health economics equation may be different in chronically transfused outpatient populations. In the REDDS trial in MDS patients, the liberal group used double the number of RBC units compared to the restrictive group over the 12-week treatment period.[39] In a detailed activity-based costing study of transfusion-dependent thalassemia patients receiving outpatient transfusion, it was estimated that the product cost of an RBC unit contributed to less than half of the total cost of administering the transfusion.[65] Apart from the direct cost of transfusion (blood product cost, hospital/staffing costs, diagnostic tests, patients' travel expenses) there are also other significant indirect costs that need to be considered in chronic disease,[66] such as the costs of reduced productivity and QoL due to symptoms of anemia or the transfusion treatment. Although health economics analyses of transfusion practice may not be broadly generalizable to all countries, given the differences in healthcare and funding models in different countries, this information may still be helpful as a starting point to enable local jurisdictions to perform their own analyses and incorporate health economics analyses into clinical trials.

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Other methodological issues with transfusion trials

The Cochrane review[6] raised the issue of lack of blinding in transfusion trials. This would depend on the choice of primary outcome –mortality is a hard endpoint and thus less susceptible to bias, however other outcomes such as QoL, physical performance, or even severity of grading of cardiovascular and other adverse events may be impacted. Although on the surface it may seem difficult to blind participants or clinicians to transfusion, the REDDS trial demonstrated successful blinding of participants to Hb level, and the majority of patients were unable to correctly guess the transfusion arm they had been allocated.[67]

The heterogeneity of patients included in trials is also an issue. In transfusion trials in cardiac patients, for example, patients with variable severity of cardiac disease or different underlying cardiac pathologies are included, which may mask potentially different effects in specific subgroups.[14]

Klein et al previously discussed the lack of a "usual care treatment group" in transfusion trials.[10] The thresholds for 'restrictive' versus 'liberal' strategies is somewhat arbitrarily allocated and applied to all trial participants and do not include other clinical or physiological factors which clinicians would usually also consider in their transfusion management. No trials have investigated whether this "usual care treatment" is in fact superior to transfusion to a Hb target alone.[10]

Finally, "standard" transfusion management has evolved in recent decades towards lower Hb transfusion thresholds which are now widely used. Future clinical trials may face the

challenge of not being able to show a significant difference in treatments if the usual care is similar to proposed new strategies, for example in trials investigating transfusion thresholds in sepsis.[68] Furthermore, clinicians themselves may perceive restrictive strategies to be superior (or equivalent) to liberal strategies for all patients, which may be a barrier for future studies.

Conclusion: Is less always best?

Many advances have been made in PBM in the last few decades, however there is still a paucity of evidence and clinical trials in chronically transfused patients, including in patients with hematological malignancies and bone marrow failure syndromes, despite the high volume of blood use in these areas. In such patients, it is unclear whether current practices such as restrictive transfusion strategies are optimal.

Patient-centred outcomes (including QoL, physical function) and health economics must be important elements of future clinical trials. Ultimately, true PBM is not simply about numbers of units of blood used, but must also focus directly on the patient, and includes patient QoL and function, and patient preferences, to optimize their transfusion management and allow best use of this precious community resource.

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