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Clinical view versus guideline adherence in ferritin monitoring and initiating iron chelation therapy in patients with myelodysplastic syndromes

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Abstract

Objectives: In patients with myelodysplastic syndromes (MDS) with >20 transfusions and ferritin levels >1000 µg/L, international guidelines recommend iron chelation therapy (ICT). The study's objective was to determine guideline adherence and the intensity of ferritin monitoring in clinical practice.

Methods: We performed an observational population-based study using the HemoBase Registry, which contains data of all MDS patients diagnosed since 2005 in Friesland, the Netherlands. Clinical information on transfusions, ferritin measurements, ICT, and clinical performance as defined by age ≤ 80 years, Charlson Comorbidity Index <2 and lower-risk MDS was collected from health records.

Results: Two hundred and thirty seven of 292 patients (81.1%) received ≥1 transfusion, and 121 (41.4%) received >20 transfusions. In 57 of these 121 patients (47.1%), ferritin measurements were performed at least once. Clinical performance was significantly associated with monitoring ferritin around the 20th transfusion (RR: 2.49, $p = .016$). Clinical performance was also associated with initiating ICT (RR: 5.99, $p < .001$). ICT was offered to 22.3% ($n = 25$) of eligible patients.

Conclusions: In this population-based study, ferritin levels were measured in <50% of MDS patients who received >20 transfusions, and clinical performance was significantly associated with measuring ferritin. Our study suggests that in heavily transfused MDS patients, ferritin monitoring is primarily based on patients' clinical performance rather than guideline recommendations.

KEYWORDS

ferritin, iron overload, myelodysplastic syndromes, population-based

Johanne Rozema and Ivar van Asten contributed equally to this work.

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1 | INTRODUCTION

Myelodysplastic syndromes (MDS) are a group of bone marrow disorders characterised by cytopenias and dysplasias.^{1,2} Treatment of anaemia includes erythropoiesis-stimulating agents (ESAs), lenalidomide, luspatercept and red blood cell (RBC) transfusions to improve anaemia-related symptoms.²⁻⁴ The majority of MDS patients require regular blood transfusions and become transfusion dependent.^{2,5} Blood transfusions temporarily alleviate anaemia-related symptoms but can be accompanied by infections, alloimmunisation, or iron overload, especially with frequent transfusions.⁶⁻⁹

Iron overload in MDS patients may be a result of two main mechanisms. First, due to impaired haematopoiesis, hepcidin levels are suppressed, which leads to increased iron absorption from the gastro-intestinal tract.⁹⁻¹⁴ Secondly, iron overload occurs due to the inability to excrete the excess iron transfused with each RBC unit (approximately 200–250 mg of iron).^{10,11,15,16} In comparison, under physiological conditions, the human body contains about 3–4 g of iron, of which only 1–2 mg is absorbed and excreted daily.^{9-11,15} Several studies have shown that iron overload is likely to occur after ≥ 20 RBC transfusions.^{8,11,17,18} Iron overload may induce the production of reactive oxygen species, which can cause chronic damage to cells and DNA as well as organ damage, including heart and liver failure or diabetes mellitus.^{9-13,19}

For the monitoring of iron (over)load, plasma ferritin levels can be assessed. Approximately 50% of iron is incorporated into haemoglobin, whereas about 25% is stored as ferritin in the liver.^{11,13,20} Ferritin is an acute phase protein, but plasma ferritin levels are well correlated with the total body iron storage. Measurement of plasma ferritin levels is an easy and inexpensive way to monitor iron storage in MDS patients.^{8,12,17} Plasma ferritin levels above 1000 $\mu\text{g/L}$ are indicative of iron overload.^{8,9,12,17,18} For MDS patients with plasma ferritin levels above 1000 $\mu\text{g/L}$, who have received >20 RBC transfusions or are transfusion dependent, (inter)national guidelines recommend the initiation of iron chelation therapy (ICT) to reduce potential organ damage from transfusion-mediated iron overload.^{11,21,22}

The aim of this study was to evaluate the adherence to (inter)national guidelines in HemoBase, a population-based registry for haemato-oncological patients.^{23,24} We determined to what extent plasma ferritin levels were monitored in MDS patients in daily practice and which patient characteristics contributed to monitoring plasma ferritin levels in the daily clinical setting.

2 | MATERIALS AND METHODS

A retrospective, population-based study was performed using the HemoBase population registry.^{7,23} HemoBase includes all haemato-oncological patients diagnosed since 2005 in Friesland, a province in the Netherlands with approximately 650 000 inhabitants. It includes patients from four general hospitals and one

medical teaching hospital. These patients are discussed in multidisciplinary meetings with the participation of haematologists from both the general hospitals and the medical teaching hospital. All persons diagnosed with MDS between 1 January 2005 and 31 December 2017 were identified for this study and retrospectively followed from the date of diagnosis through March 2019. Their diagnosis was confirmed by an expert panel according to the World Health Organization 2016 classification.^{1,7} Clinical information on transfusions, plasma ferritin levels, and ICT as well as patient characteristics were collected from health records and laboratory systems. The Medical Ethics Committee in Leeuwarden confirmed the study execution without the need for ethical review, and the institutional boards approved the study execution without the need for consent in accordance with Dutch regulations and the Declaration of Helsinki (2013 revision).

To investigate the number of plasma ferritin measurements, only patients who received ≥ 1 transfusion were included. Plasma ferritin was measured with an immuno-assay on a Roche (Roche Diagnostics GmbH, Mannheim, Germany) or Beckman Coulter (Beckman Coulter Life Sciences, Indianapolis, IN, USA) chemistry analyser according to the manufacturer's protocol. Measurements >1 month after the last transfusion were not considered, as for this study we were only interested in measurements of plasma ferritin levels whilst receiving transfusions, and it was assumed that these measurements were no longer performed to monitor transfusion-mediated iron overload. The national guidelines state that after receiving >20 RBC units, iron overload may occur, and monitoring should be performed.¹⁸ Therefore, as a measure of adequate guideline adherence, we defined a "per-guideline measurement" as a plasma ferritin measurement performed between the 15th and 25th transfusion. In addition, we evaluated whether plasma ferritin measurements were performed at any moment in time after the 20th transfusion in patients receiving >20 transfusions.

Transfusions were given to the patients according to the national guidelines.¹⁸ The revised International Prognostic Scoring System (IPSS-R) score, Charlson Comorbidity Index (CCI) score, and patient age were studied to determine whether these factors contribute to the measurement of plasma ferritin levels in clinical practice. MDS patients with an IPSS-R score of (very) low, or intermediate, were categorised as lower-risk MDS and patients with a score of (very) high as higher-risk MDS.^{25,26} Patients who did not meet the IPSS-R criteria due to missing cytogenetic data or unsuccessful bone marrow biopsies were presented as a separate category. The CCI was used to assess patients' comorbidities.²⁷ A CCI score of 0 indicated no relevant comorbidities. It was hypothesised that in fit patients, ferritin monitoring and ICT may be more often initiated. Clinical performance was included as a parameter to test this assumption. Good clinical performance was arbitrarily defined as having >1 of the following factors: age ≤ 80 years, CCI score <2 , and lower-risk MDS. The national guideline states that ICT should be initiated in patients with a life expectancy of >1 year and with plasma ferritin levels $>1000 \mu\text{g/L}$ or when a patient receives >20 transfusions.¹⁸ In this study, patients with an IPSS-R score of very



low, low, intermediate, or high were considered to have a life expectancy of >1 year.²⁶ Logistic regression analyses were performed using IBM SPSS v.24 to analyse the relative risks (RR) of monitoring plasma ferritin levels for different patient characteristics.

2.1 | Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

3 | RESULTS

3.1 | Monitoring of plasma ferritin levels

In total, 237 of 292 identified MDS patients (81.1%) received at least one transfusion (Table 1). The median follow-up was 21.8 months (95% CI: 18.0–25.5), the majority of the population was male (69.2%), and the median age was 76.0 years (range: 27.5–92.0) (Table 1). Overall, 121 patients received more than 20 RBC transfusions (51.1%). Plasma ferritin measurements were performed in 57 of 121 patients (47.1%, Figure 1), with a median of two measurements per patient (range: 1–13, Table 2). In 47 of these 57 patients (82.5%), a plasma ferritin level of > 1000 µg/L was detected (range: 1129–9036 µg/L).

3.2 | Indicators for ferritin measurements

In patients with >20 transfusions, no significant differences were observed in measuring plasma ferritin levels between the 15th and 25th transfusion for different age groups, CCI scores, or IPSS-R risk groups, with $RR_{\text{age}\leq 80}$: 1.51 (95% CI: 0.71–3.19, $p = .28$); $RR_{\text{CCI}<2}$: 1.46 (95% CI: 0.78–2.73, $p = .24$); $RR_{\text{low IPSS-R}}$: 1.42 (95% CI: 0.60–3.39, $p = .43$); and $RR_{\text{unknown IPSS-R}}$: 0.96 (95% CI: 0.37–2.54, $p = .94$), respectively (Table 3). Clinical performance was significantly associated with an increased probability of monitoring plasma ferritin levels between the 15th and 25th transfusion ($RR_{\text{clinical performance}}$: 2.49, 95% CI: 1.18–5.25, $p = .02$) (Table 3). During the complete follow-up of patients who received more than 20 blood transfusions, clinical performance was also significantly associated with an increased probability of monitoring plasma ferritin after the 20th blood transfusion, with $RR_{\text{clinical performance}}$: 2.16 (95% CI: 1.35–3.45, $p = .001$) (Table 3).

3.3 | Iron chelation therapy

Guideline adherence for initiating ICT was assessed by studying the prescription of ICT according to national guidelines.¹⁸ In our population, 112 of 237 patients (47.3%) fulfilled the criteria for initiation. ICT was prescribed to 25 of these patients (22.3%). Meanwhile, five of

TABLE 1 Patient characteristics

	Patients with 1–20 RBC N (%)	Patients with >20 RBC N (%)
Total	116 (100)	121 (100)
Follow-up (years, median [95%CI])	18.2 (13.0–24.9)	23.8 (19.8–30.1)
Male	75 (64.7)	89 (73.6)
Age at diagnosis (years, median [range])	75.9 (36.8–92.0)	76.2 (27.5–91.7)
Hospital		
Medical teaching hospital	58 (50.0)	66 (54.5)
General hospital	58 (50.0)	55 (45.5)
MDS subtype		
SLD	15 (12.9)	16 (13.2)
MLD	17 (14.7)	17 (14.0)
RS-SLD	26 (22.4)	12 (9.9)
RS-MLD	13 (11.2)	9 (7.4)
Del5q	1 (0.9)	4 (3.3)
EB-1	19 (16.4)	25 (20.7)
EB-2	12 (10.3)	23 (19.0)
U	3 (2.6)	2 (1.7)
n.o.s.	10 (8.6)	13 (10.7)
IPSS-R		
Lower Risk	63 (54.3)	55 (45.5)
Very Low	10 (8.6)	7 (5.8)
Low	34 (29.3)	33 (27.3)
Intermediate	19 (16.4)	15 (12.4)
Higher Risk	11 (9.5)	23 (19.0)
High	5 (4.3)	14 (11.6)
Very High	6 (5.2)	9 (7.4)
Unknown	42 (36.2)	43 (35.5)
CCI score		
0	28 (24.1)	43 (35.5)
1	27 (23.3)	20 (16.5)
2–3	24 (20.7)	33 (27.3)
≥4	34 (29.3)	25 (20.7)
Unknown	3 (2.6)	0 (0)
ICT	7 (6.0)	23 (19.0)

Abbreviations: CCI, Charlson Comorbidity Index; Del5q, Deletion of chromosome 5q; EB, Excess blasts; ICT, Iron chelation therapy; IPSS-R, Revised International Prognostic Scoring System; MDS, Myelodysplastic syndromes; MLD, Multilineage dysplasia; n.o.s., Not otherwise specified; RBC, Red blood cells; RS, Ring sideroblasts; SLD, Single lineage dysplasia; U, Unclassified.

237 patients (2.1%) received ICT whilst not fulfilling the criteria (i.e., low life expectancy, low transfusion burden, and/or ferritin <1000 µg/L). Plasma ferritin levels were monitored in 18 patients (60.0%) during ICT. In four patients (13.3%) on ICT, plasma ferritin levels were never measured.

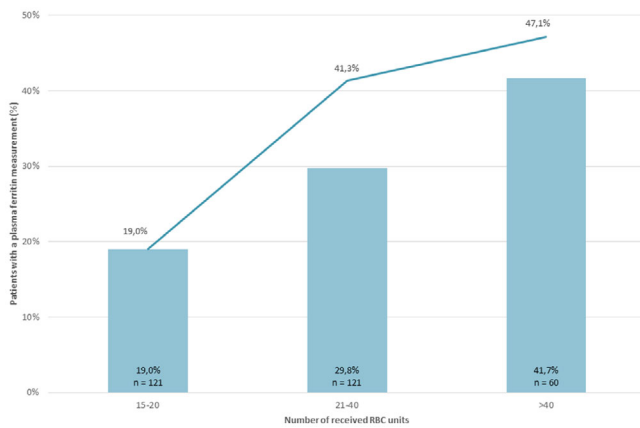


FIGURE 1 Plasma ferritin measurements in patients with myelodysplastic syndromes who received >20 transfusions. The bars represent the number of patients with a measurement between 15–20 transfusions, between 21–40 transfusions, and after they received >40 transfusions. The cumulative number represents the total number of patients with at least one plasma ferritin measurement since their 15th transfusion

TABLE 2 The number of ferritin measurements before and after 20 RBC transfusions

	1–20 RBC N (%)	>20 RBC N (%)
Total no. of patients	237 (100)	121 (100)
No. of ferritin measurements		
0	118 (49.8)	71 (58.7)
1	46 (19.4)	21 (17.4)
2	30 (12.7)	10 (8.3)
≥3	43 (18.1)	19 (15.7)
Median no. of ferritin measurements		
Median (all)	1 (0–27)	0 (0–13)
Median (≥1) ^a	2 (1–27)	2 (1–13)

^aExcluded patients without any plasma ferritin measurement.

TABLE 3 The relative risks for plasma ferritin monitoring around the 20th transfusion and after >20 transfusions in patients who received >20 transfusions

		N (%)	15–25 RBC RR (95% CI)	p-value	N (%)	>20 RBC RR (95% CI)	p-value
Age at diagnosis	>80 y	37 (30.6)	Ref.		37 (30.6)	Ref.	
	≤80 y	84 (69.4)	1.51 (0.71–3.19)	.28	84 (69.4)	1.76 (0.99–3.13)	0.054
CCI score	≥2	58 (47.9)	Ref.		58 (47.9)	Ref.	
	<2	63 (52.1)	1.46 (0.78–2.73)	.24	63 (52.1)	1.00 (0.65–1.53)	.99
IPSS-R score	Higher risk	23 (19.0)	Ref. ^a		23 (19.0)	Ref. ^b	
	Lower risk	55 (45.5)	1.42 (0.60–3.39)	.43	55 (45.5)	1.91 (0.99–3.69)	.053
	Unk.	43 (35.5)	0.96 (0.37–2.54)	.94	43 (35.5)	0.84 (0.38–1.87)	.67
Clinical performance	0–1 factor (good)	53 (43.8)	Ref.		53 (43.8)	Ref.	
	2 factors	42 (34.7)	1.54 (0.71–3.37)	.28	42 (34.7)	1.11 (0.63–1.96)	.71
	3 factors (poor)	26 (21.5)	2.49 (1.18–5.25)	.016	26 (21.5)	2.16 (1.35–3.45)	.001

Abbreviations: CCI, Charlson comorbidity index; CI, Confidence interval; IPSS-R, Revised International Prognostic Scoring System; RBC, Red blood cell units; RR, Relative risk; Ref, Reference group; Unk, Unknown; y, Years.

^aOverall p-value for IPSS-R = 0.48.

^bOverall p-value for IPSS-R = 0.005.

To determine which factors were associated with initiating ICT, univariate analyses were performed. There were no significant differences in gender, hospital type, and CCI score, but age < 80 years and lower-risk IPSS-R were significantly associated with an increased probability of initiating ICT (RR_{age<80}: 2.65, 95%CI: 1.05–6.65, $p = .04$; RR_{low IPSS-R}: 3.60, 95%CI: 0.90–14.4, $p = .07$; and RR_{unknown IPSS-R}: 0.60, 95%CI: 0.10–3.43, $p = .57$, respectively). Moreover, patients with good clinical performance were treated with ICT more often compared to patients with poor clinical performance: 29.6% versus 7.7%, respectively (RR_{clinical performance}: 5.99, 95%CI: 2.32–15.45, $p < .001$) (Table 4).

4 | DISCUSSION

This study showed that plasma ferritin levels were measured in 47.1% of MDS patients who received more than 20 blood transfusions, and in the majority of these patients, plasma ferritin levels were above 1000 µg/L. Only a minority of all eligible patients for ICT received it, and the response to ICT through monitoring plasma ferritin levels was not accurately assessed. Good clinical performance, as defined by age ≤ 80 years, CCI score <2, and lower-risk MDS, was significantly associated with an increased probability of measuring plasma ferritin in patients with >20 transfusions, and patients with good clinical performance more often received ICT.

The literature, alongside national and international guidelines, recommends starting ICT in MDS patients after they have received 20–25 RBC units due to the risk of transfusion-induced iron overload.^{9,16,18,22,28} A survey amongst treating haematologists showed that receiving 20–29 RBC transfusions and reaching a plasma ferritin level > 1000 µg/L were considered important factors for starting ICT.²¹ However, as shown in our study reflecting daily clinical practice, the monitoring of plasma ferritin levels was not performed routinely nor was initiating ICT. Therefore, our study suggests that



		N (%)	RR (95% CI)	p-value
Hospital type	Medical teaching	124 (52.3)	Ref.	
	General	113 (47.7)	1.44 (0.73–2.82)	.29
Gender	Female	73 (30.8)	Ref.	
	Male	164 (69.2)	1.29 (0.52–3.20)	.58
Age at diagnosis	>80 y	82 (34.6)	Ref.	
	≤80 y	155 (65.4)	2.65 (1.05–6.65)	.039
CCI score	≥2	116 (49.6)	Ref.	
	<2	118 (50.4)	1.70 (0.85–3.41)	.14
IPSS-R score	Higher risk	34 (14.3)	Ref. ^a	
	Lower risk	118 (49.8)	3.60 (0.90–14.4)	.07
	Unk.	85 (35.9)	0.60 (0.10–3.43)	.57
Clinical performance	0–1 factor (good)	101 (42.6)	Ref.	
	2 factors	82 (34.6)	2.22 (0.77–6.36)	.14
	3 factors (poor)	54 (22.8)	5.99 (2.32–15.45)	<.001

Abbreviations: CCI, Charlson comorbidity index; CI, Confidence interval; IPSS-R, Revised International Prognostic Scoring System; RR, Relative risk; Unk, Unknown; Ref, Reference group; y, Years.

^aOverall p-value for IPSS-R = 0.003.

transfusion-related iron overload may be under-recognized by haematologists in their MDS patients.²⁹ It has been described that iron overload is correlated with decreased survival, higher incidence of infections, ineffective erythropoiesis and an increased risk of leukemic transformation of MDS due to genomic alterations.^{9,19,30–32} The TEL-ESTO study showed positive clinical effects of ICT in lower-risk MDS patients, and another study noted better overall survival amongst patients who received ICT as recommended by guidelines; better monitoring of potential iron overload might therefore prevent iron overload-related effects that impair patient life expectancy.^{9,19,31}

In our study population, the decision to initiate ICT was most likely influenced by the clinical performance of patients. Patients with a long(er) life expectancy may be more prone to organ damage caused by iron overload and could therefore benefit more from ICT compared to patients with a relatively short life expectancy.^{19,28} ICT is especially accepted in lower-risk MDS patients, but may also be beneficial in higher-risk MDS patients that are eligible for allogeneic stem cell transplantation or in patients responding to hypomethylating agents.^{9,28,33,34} Recent research reported similar ICT safety and efficacy in higher-risk MDS patients compared to lower-risk MDS patients.³³ Although this retrospective analysis was performed in a small higher-risk MDS population, it indicates that monitoring potential iron overload is relevant in this patient group, especially since the life expectancy of higher-risk MDS patients is improving.^{9,32,33} Because it is unclear whether the benefits of ICT outweigh its side-effects in MDS patients and due to the costs of ICT, treating haematologists seem reluctant in providing ICT in MDS patients.^{19,21,29} In this study, plasma ferritin levels were monitored more frequently in patients <80 years of age or with lower-risk MDS after receiving more than 20 transfusions, and it appears that fitter patients, also represented in clinical performance, were more likely to be monitored for potential iron overload. Our study suggests that the clinical

performance of individual patients and the clinical view of the treating haematologist is predominant in initiating ferritin monitoring or ICT.

Recently, the revised national transfusion guidelines were published, which offers room for the physician to make more personalised considerations and underscores the importance of the clinical assessment.³⁵ A recent study acknowledged the option for shared decision-making in MDS patients.³¹ In clinical practice, decision making is likely to be more tailored to an individual patient than solely based on the IPSS-R score, comorbidities, and age. For instance, quality of life and patients' motivations for therapy may play a role. This information cannot be retrospectively extracted from our database but may have contributed to the discrepancy between clinical practise and guideline recommendations. Nevertheless, when ICT is initiated, plasma ferritin levels should be monitored in all patients to evaluate the treatment response. Periodical notifications to check whether plasma ferritin monitoring and ICT are indicated might be helpful, and we recommend testing this principle in future studies. In addition, future research is required to illustrate whether clinical perspective results in better patient outcomes than strict guideline adherence.³¹

This study is, to the best of our knowledge, the first that reviews the monitoring of plasma ferritin levels in MDS patients in daily clinical practise. As this was a retrospective study, physicians' behaviour was not influenced by study participation. In addition, the HemoBase registry ensured a population-based setting for multicentre research over a long-term follow-up period, including detailed information on transfusions and ferritin measurements. This study therefore provides representative results for the management of ferritin levels in MDS patients in the Netherlands. These results should be confirmed in other communities before extrapolating to other countries.

However, we could not accurately examine the original purpose of the measurement nor the physician (or type of expertise) who ordered it (e.g., treating haematologist or family practitioner) due to

TABLE 4 The relative risks for initiating ICT



the retrospective design of the study. Therefore, our analysis of monitoring plasma ferritin levels as a result of dedicated monitoring related to the patient's transfusion burden could be an overestimation, and real numbers may potentially be lower, as measurements could have been performed with a clinical rationale other than MDS. Additionally, we were unable to identify whether all transfusions were given for MDS-related anaemia. However, regardless of the indication of received transfusions, iron overload may still occur. In this study, we used plasma ferritin as a measure of potential iron overload, but due to the study's design, we were unable to investigate which patients developed iron overload-induced organ damage. Moreover, the effect of ICT in heavily transfused MDS patients on improving quality of life and reducing iron-induced organ damage is unknown.¹⁹ Nevertheless, plasma ferritin levels should be monitored more often to optimise decision-making regarding ICT and potential iron overload.

5 | CONCLUSION

In this population-based study, plasma ferritin levels were measured in less than 50% of MDS patients with more than 20 transfusions. A minority of all eligible patients received ICT, and the monitoring of plasma ferritin levels during ICT was not regularly performed. Our results indicate that the monitoring of plasma ferritin levels is mainly based on clinical perspective rather than guideline adherence. The ferritin monitoring in our study may be an overestimation, as measurements could have been performed with a clinical rationale other than MDS. Future research is required to illustrate whether clinical perspective results can improve patient outcomes more than strict guideline adherence.

AUTHOR CONTRIBUTIONS

Johanne Rozema, Ivar van Asten, Eric N. van Roon, Mels Hoogendoorn, Robby E. Kibbelaar, and Harry de Wit designed the project. Johanne Rozema, Ivar van Asten, and Beau Kwant collected the data. Johanne Rozema, Beau Kwant, and Nic J. G. M. Veeger analysed the data. Johanne Rozema and Ivar van Asten wrote the manuscript. Eric N. van Roon, Mels Hoogendoorn, Robby E. Kibbelaar, Harry de Wit, and Nic J. G. M. Veeger provided input in data analysis. All authors contributed to critical revision and gave final approval of the manuscript.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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