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Prevalence and Factors associated with Platelet Refractoriness among Tanzanian Patients – A Cross-Sectional Study from The National Reference Hospital

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Abstract

Background

A response to platelet transfusion is assessed by post transfusion platelet increment and failure to reach a desired increment is termed platelet refractoriness, which is best measured by the corrected count increment (CCI) which takes into account the dose of platelets transfused, weight and height. The causes of platelet refractoriness can be immune or non-immune. In Tanzania, platelet refractoriness has not yet been evaluated. Therefore, we examined the prevalence of platelet refractoriness and factors affecting platelet refractoriness among patients admitted to the national referral hospital in Tanzania.

Methods

We conducted a cross-sectional study on 161 hospitalized patients above one year of age who were diagnosed with conditions that may potentially require platelet transfusion. A standardized clinical record form was used to collect information on demographic characteristics and the patients' clinical conditions. Pre- and post-transfusion platelet counts (one hour and 24 hours post-transfusion) were checked to compute the CCI. A total of 51 single donor platelet concentrates were analysed to assess their quality in terms of platelet count.

Results

Most of the 51 platelet concentrates were of sufficient quality as the majority (48; 96%) had a count of > 5.5 x 10^9 platelets per concentrate and 48 (96%) also had a residual white cell count of < 0.8 cells/mL. Of the 161 patients who received platelet transfusion, the proportion with platelet refractoriness was 28%. Among several factors, fever was the only factor significantly associated with platelet refractoriness, with an adjusted odds ratio of 10.98 (95% CI 3.93 - 30.66; p<0.001).

Conclusion

The platelet concentrates prepared at our hospital had good quality, and conformed to the guidelines of Tanzania National Blood Transfusion Services and the Association for the Advancement of Blood & Biotherapies in the US. Platelet refractoriness was found in almost one-third of the patients and was strongly associated with fever.

Keywords: *Bleeding, Fever, Platelet count, Thrombocytopenia, Transfusion.*

Introduction

Platelet transfusions are essential in the management of many thrombocytopenic patients (1-3). Platelet concentrates can be derived from a single donor by apheresis or from whole blood. So-called buffy coat platelet concentrates are prepared from fresh, whole blood by high-spin centrifugation, removing the supernatant (platelet poor plasma) and the red blood cells (RBCs) (4-7). Based on their preparation, the platelet concentrates can be derived from either single donor, pooled random donors or from apheresis. In our setting, we use single donor platelet concentrates.

The quality of a platelet concentrate is assessed through various parameters, including the volume of the concentrate, the platelet count itself, and contamination with residual RBC and white blood cells (WBC). According to the Association for the Advancement of Blood & Biotherapies in the US (AABB), a unit of platelet concentrate derived from whole blood should contain ≥ 5.5 x 10^{10} platelets in 40–70 mL of plasma, with residual white blood cells (WBC) of less than 0.83 x10^{6} (8). In Kenya, Onchaga et al conducted a study at Nairobi Regional Blood Centre and showed that 95.6% and 79.1% met the AABB-criteria on platelet count and residual WBC, respectively (9). However, another Kenyan study by Thuku et al in Kenyatta National Hospital, revealed that only 65% met these criteria (10). A similar study in Nigeria showed that only 35% of the platelet concentrates had platelet counts > 5.5 × 10^{10}, pointing to the need to improve the quality of the preparations of platelet concentrates in low-resource settings (5). In Tanzania, only single donor platelets are produced in tertiary hospitals and the Tanzania National Blood Transfusion Services (TNBTS) recommends a minimum platelet count of 5.5 ×10^{9} in 50 mL of platelet concentrate, even though there are no studies done to evaluate the quality of these platelet concentrates (11).

According to the TNBTS' guideline, therapeutic platelet transfusion is indicated in patients with bleeding and platelet counts < 50,000/µL. Prophylactic transfusion is indicated in patients with platelet count of < 10,000/µL, or < 20,000/µL with other risk factors for bleeding (e.g. fever, anemia, sepsis, disseminated intravascular coagulation (DIC), and certain drugs) (11).

Platelet transfusion is also indicated in patients undergoing surgery with platelet counts < 50,000/µL, and those undergoing critical surgery (e.g. cardiopulmonary bypass surgery, neuro- and ophthalmology surgeries) with platelet counts < 100,000/µL. For massive transfusion needs, platelet transfusion is required to maintain platelet counts ≥ 50,000/µL, and in those with multiple trauma and head injury, platelet transfusion is given to maintain platelet counts >100,000/µL (11,12). However, the majority of patients receiving platelet transfusions are those with hemato-oncologic conditions (13). Notably, inappropriate platelet

transfusions (i.e. transfusions that do not align with guidelines) are not uncommon in low-resource settings (14,15).

Response to platelet transfusion is assessed by post transfusion platelet increment and failure to reach a desired increment is termed platelet refractoriness (16,17). Platelet refractoriness is affected by a number of factors which are classified into the two major categories of immune and non-immune factors (6). Immune factors include anti-HLA antibodies and anti-HPA antibodies. Non-immune factors include fever, sepsis, disseminated intravascular coagulation, drugs (such as amphotericin B, anti-thymocyte globulin and vancomycin), splenomegaly and the number of previous transfusions. The post transfusion increment is also affected by the platelet concentrate storage time, blood group ABO compatibility and the number of platelets in a unit of a platelet concentrate (17-19).

Corrected count increment (CCI) is a more precise formula to assess platelet refractoriness since it takes into account the number of platelets transfused and the recipient's body surface area (18,20,21). A CCI below 5000 indicates platelet refractoriness. The TRAP Study identified fever (≥ 38.4°C), increased number of platelet transfusions, heparin administration, bleeding, increased body weight, history of at least two pregnancies or male gender, as variables associated with increased risk of platelet refractoriness (22). On the other hand, ABO-identical platelets and platelets stored for less than 3 days contributed to a higher CCI (23).

The scarcity of blood products has been well documented by the TNBTS, particularly with platelet concentrates (11). Importantly, in Tanzania, platelet concentrates have been used for years, but its effectiveness in terms of post transfusion increment has not yet been evaluated. This study was therefore performed to examine the prevalence of platelet refractoriness and factors affecting platelet refractoriness among patients admitted at Muhimbili National Hospital (MNH) in Dar-es-Salaam, the national referral hospital in Tanzania.

Methods

Study design, study setting and study participants

This cross-sectional study was conducted between October 2019 and January 2020 at MNH, which is the national referral hospital in the Tanzania and receives patients referred from all regional hospitals. MNH has a blood bank which prepares platelet concentrates from freshly donated blood (less than 8 hours after collection). The platelet concentrates were prepared according to the standards of the TNBTS. In brief, platelet-rich plasma was obtained through centrifugation at low spin (2500 rpm) for 10 minutes at room temperature

before a high spin centrifugation (3500 rpm) for 10 minutes before separation using a plasma extractor. Then they were stored in agitator for a maximum of five days. About 400 to 600 platelet concentrates are prepared and issued to approximately 100 to 200 patients per month. In this study, all patients above the age of one year admitted to MNH and who received platelet transfusion were included whereas those with immune thrombocytopenia (ITP) were excluded.

Sample size calculation

A sample size of n = 161 patients for the study was calculated based on an expected proportion of platelet refractoriness (as estimated from other studies to be 25% (24) and a margin of error (precision) of 5%. These patients were identified from the blood bank and contacted in the respective wards. Fifty-one platelet concentrates were assessed for quality and they were selected through a systematic sampling technique, i.e. every 5th platelet concentrate that was prepared was included in the study.

Data collection

The study patients were recruited from all inpatient wards at MNH. Patient information was collected using a standardized clinical record form that covered demographic information, medical diagnosis, drug history, presence or absence of splenomegaly, previous history of pregnancy, previous transfusion history and indication for platelet transfusion. Additional information was obtained from the patients' medical records and physical examination of the patient.

Pre- and post transfusion platelet counts were obtained by collecting patient samples (2 mL of blood) in EDTA tubes and performing complete blood count (CBC) by CELL DYN Ruby Haem Analyser (Abbot, Abbott Park, Illinois, USA) at 1 and at 24 hours post transfusion.

A patient having body temperature above 38.5˚C within 24 hours following a platelet transfusion, was considered as febrile (16-18). The participants were considered to have infection if they had a confirmed microbial diagnosis in the current admission and/or elevated C-reactive protein concentration (above 10 mg/L). Bleeding was assessed clinically and graded according to the WHO scale (12). A palpable spleen was considered as splenomegaly.

Information of blood group and storage days of the platelet concentrates was obtained from the platelet pack-labels. The weight of the platelet concentrates was obtained and their volumes were computed. Platelet count per unit of platelet concentrate was analysed in a 2 mL sample using the CELL DYN Ruby Haem Analyser.

Determination of corrected count increment

We used the MD Calc software (25) to compute the corrected count increment (CCI), i.e. the difference between the post- and pre-transfusion platelet counts multiplied with the body surface area (BSA) and divided with the number of transfused platelets:

$$CCI = \frac{\text{(Post-transfusion count – Pre-transfusion count)}/\mu L \times BSA\ (m^2)}{\text{Number of transfused platelets}}$$

The CCI was compared to the standard value, which is supposed to be ≥ 7500 at 1 hour and ≥ 5000 after 24 hours, and lower values were considered as platelet refractoriness (18).

Statistical analyses

For the demographic data, proportions were calculated. Bivariate (unadjusted) analysis was performed to examine possible factors affecting platelet refractoriness. Those factors with significant associations from the bivariate analysis (p value less than 0.2) were then included in a multivariate (adjusted) logistic regression model. A p-value of less than 0.05 was regarded as significant. SPSS version 20.0 statistical software was used.

Approvals

Ethical approval was given from the Research and Publications' Committee of Muhimbili University Hospital and Allied Sciences. Permission to conduct the study was approved by MNH. Written informed consent was obtained from the adults (> 18 years), assent was obtained for participants aged 13 to 17 years, and for those below 13 years, written consent was obtained from parents/guardians.

Results

Characteristics of the study patients

We assessed 192 patients for eligibility. Among these, 22 were below one year and 9 had ITP, leaving 161 for further analyses. Table 1 shows their clinical characteristics. The patient median (interquartile range) age was 16 (7-35) years, and 75 (46.6%) were children (≤14 years) whereas males constituted 75 (47%). Most patients had acute leukemia (n=54; 33.5%) or aplastic anemia (n=40; 24.8%). Other diagnosis included surgical conditions requiring platelet transfusion, HELLP syndrome and preeclampsia. Most patients (n=108; 67%). were transfused either to stop bleeding, or prophylactic against bleeding as per the guidelines of TNBTS. Thirty-four (21%) were transfused with no clear documented indication, thus not adhering to the prevailing transfusion guidelines.

Table 1: Clinical characteristics of the 161 study participants

Characteristic	Number	Percentage
Age-group		
Age < 14 years[1]	75	46.6
Age ≥ 14 years	86	53.4
Gender		
Male	75	47
Female	86	53
Primary diagnosis		
Aplastic anemia	40	24.8
Acute leukemia	54	33.5
Solid malignancies	24	14.9
Other diagnoses[2]	43	26.7
Indications for platelet transfusion		
Bleeding	54	33.5
Prophylaxis	54	33.5
Surgery	13	8.1
No clear indication	34	21.1
DIC	6	3.7
History of previous blood transfusion	151	93.8
History of previous platelet transfusion	65	40.4
Presence of splenomegaly	32	19.9
Presence of infection	86	53.4
High CRP (> 10 mg/L)	127	78.9
History of pregnancy	34	72.3%
History of bleeding during the current admission	69	42.9
WHO bleeding score		
Grade 0	92	57.1
Grade 1	4	2.5
Grade 2	43	26.7
Grade 3	22	13.7
Grade 4	0	0
Fever within 24 hours	26	16.1

[1]Those < 14 years were defined as pediatric patients. [2] Other diagnosis included surgical conditions requiring platelet transfusion, HELLP syndrome and preeclampsia. DIC: Disseminated intravascular coagulation; CRP: C reactive protein.

Quality of platelet concentrates

Fifty-one platelet concentrates were evaluated for platelet quality. The quality parameters which were assessed included the platelet count, residual WBC, residual RBC and the volume of the platelet concentrate. Other parameters were not assessed due to lack of

appropriate testing kits/equipment. The quality of platelet concentrate was measured at day one of storage (Table 2). The majority of the platelet concentrates (n=48, 96%), had platelet counts ≥ 5.5 x 10^9, hence met the TNBTS criteria. Similarly, 48 (96%) platelet concentrates met the AABB criteria for residual WBC of < 0.8 x 10^6 cells/mL.

Table 2: Quality parameters of the platelet concentrates

Parameter			Mean ± SD or median (IQR)
	Minimum	Maximum	
Platelet count (x10^9)	0.9	140	53.9 ± 29.9
Residual WBC (per mL)	0.02	5.51	0.077 (0.15)
Residual RBC (per µL)	0.00	0.72	0.043 (0.07)
Volume (mL)	46	95	70 ± 11.6

WBC: white blood cell; RBC: red blood cell; SD: standard deviation;
IQR: interquartile range.

Proportion of platelet refractoriness among the study patients

A total of 581 platelet concentrates were transfused to the 161 patients during the study period. The mean (± SD) number of platelet concentrates given to each of them was 3.6 ±1.4. At enrolment into the study and before any transfusion, the blood median (interquartile range) platelet concentration was 14,000 (8,500 – 36,000)/µL among the 161 participants. The response to platelet transfusion was measured by CCI at one hour and at 24 hours. Figure 1 shows the individual CCI values. Although this plot shows marked scatter in the dataset, there is a fair distinction between CCI values below and above the cut-off value of 5000. At one and 24 hours it was >7500 in 126 (78.3%) and >5000 in 116 (72%) of the study patients, respectively. Therefore, the proportion of platelet refractoriness was 28% in our study. More specifically, the proportion of platelet refractoriness was 26.7% among male and 29.1% among female patients (Table 3). Table 4 shows the number of platelet packs transfused to the patients.

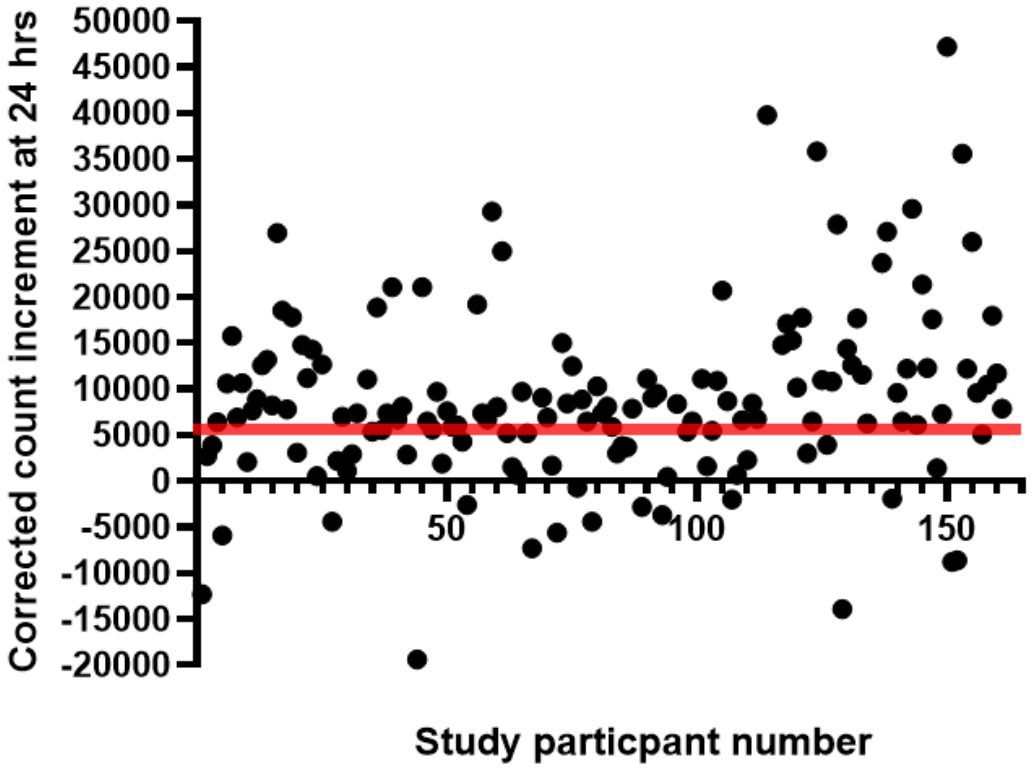

Figure 1. Corrected Count Increment for individual patients

Dot plot showing individual values (X-axis) for corrected count increment (Y-axis). Inserted are the cut-off value (5000) for platelet refractoriness (horizontal red line). Values for 30 outliers are not shown (n=20 had values below zero, i.e. post-transfusion platelet count was lower than the pre-transfusion platelet count); n=10 had values above 50 000).

Factors affecting platelet refractoriness

Next, we sought to determine factors affecting platelet refractoriness (Table 3). All participants were given platelets stored less than 3 days and all were given platelet concentrates that were ABO compatible. No participant was on amphotericin or other drugs known to impact on platelet refractoriness. Fever was found to be strongly associated with platelet refractoriness with an adjusted odds ratio of 10.79 (95% CI 3.86 – 30.16; P <0.05). Other factors like history of blood transfusion, presence of bleeding, pregnancy history and splenomegaly were not significantly associated with platelet refractoriness.

Table 3: Factors associated with platelet refractoriness

Variable	Platelet refractoriness	Crude OR	P-value	Adjusted OR	P-value
Age					
< 14 years	18/75 (28%)	Ref			
≥ 14 years	27/86 (31.4%)	1.45 (0.72-2.91)	0.29	-	-
Sex					
Male	20/75 (26.7%)	Ref			
Female	25/86 (29.1%)	1.13 (0.56-2.25)	0.73	-	-
History of blood transfusion					
No	2/10 (20%)	Ref			
Yes	43/151 (28.5%)	1.59 (0.33-7.8)	0.57	-	-
Presence of infection					
No	16/75 (21.3%)	Ref			
Yes	29/86 (33.7%)	1.88 (0.92-3.82)	0.083	1.15 (0.47 – 2.81)	0.77
Fever					
No	19/26 (|73.1%)	Ref			
Yes	26/135 (19.3%)	11.38 (4.33-29.91)	0.00	10.98 (3.93-30.66)	0.00
Presence of bleeding					
No	21/92 (22.8%)	Ref			
Yes	24/69 (34.8%)	1.83 (0.9-3.62)	0.09	1.81 (0.82-3.99)	0.14
Splenomegaly					
No	34/129 (26.4%)	Ref			
Yes	11/32 (34.4%)	1.46 (0.64-3.35)	0.37	-	-

Values are the results of bivariate (crude) and multivariate (adjusted for age, sex, history of blood transfusion and splenomegaly) analyses. Ref: Reference value; OR: Odds ratio.

Table 4: Number of platelet concentrate packs transfused to the patients

Number of platelet packs	Number of patients receiving a specific number of platelet packs
1	2
2	36
3	51
4	37
5	10
6	16

Discussion

In this study, among the 161 patients who received platelet transfusion during a period of 3 months, one third of them had platelet refractoriness. Fever was the only significant factor associated with platelet refractoriness. During the study period, all patients received ABO compatible platelets and due to scarcity of blood products, all patients received freshly prepared platelets. Notably, we found that the quality of platelet concentrates prepared at the hospital was satisfactory since nearly all (96%) tested platelet concentrates fulfilled the TNBTS criteria for platelet count in platelet concentrates.

Similar to other studies, the majority of recipients of platelet transfusion in our study were patients diagnosed with acute leukemia or aplastic anemia (14,15,26,27). Moreover, we found that the most frequent indications for platelet transfusion were for prophylaxis purposes and arresting ongoing bleeding (67%), whereas surgery (8%) and DIC (4%) were least frequent. However, inappropriate transfusion (no clear indication as per the TNBTS guidelines) was found in about 20% of the patients. This is similar to a study done in India (26), but is lower compared to reports from South Africa (38%) and New Zealand (28%) (14,27). Interestingly, in the study by Ahsan et al, the proportion of inappropriate platelet transfusion dropped from 20% to 1% in a period of one year following implementation of platelet transfusion guidelines (12). Notably, we expect that when stem cell transplantation is introduced in Tanzania, the demand for platelet concentrates will be higher (28). Moreover, inappropriate transfusion of platelet concentrates has been associated with increased demand of platelets and has cost implications to the overall health care system, as shown by Sonnekus et al (14). In our study, 10.4% of participants received suboptimal numbers of platelet concentrates due to scarcity of the components. In 2013, TNBTS surveyed the utilisation of blood component and found that platelet transfusion accounted for 1.4% of the blood components (29). Despite this being a small percentage, there is still scarcity of these components nationally. Appropriate use of these products will thus most likely serve to reduce demand and enable optimal use of platelet concentrates.

The proportion of platelet refractoriness (28%) in our study was lower compared to a study done in Kenya by Thuku et al which showed that 70% of males and 75% of females had platelet refractoriness (10), whereas the corresponding proportions in our study were 26.7% and 29%, respectively. Notably, these two studies included the same age group. In our study, factors that might have attributed to the lower proportion of refractoriness include the transfusion of fresh platelets (i.e. stored for less than 3 days) and transfusion of ABO compatible platelets as well as exclusion of patients with ITP.

Transfusion of ABO compatible platelets reduces the prevalence of platelet refractoriness (16,21,30-32). Corroborating this, a study done in children by Julmy et al showed that transfusion of ABO major mismatched platelets resulted in poor post transfusion platelet increment (32). Interestingly, it has been demonstrated that platelets of donors with blood group A will be rapidly cleared from the circulation among blood group O/B recipients (30,32). In line with this, Panvenski et al found a reduction of approximately 20% in platelet refractoriness among patients who received ABO compatible platelets (33). Also, transfusion of fresh platelets has been shown to increase post transfusion platelet increment (34).

Fever was strongly associated with platelet refractoriness with an adjusted odds ratio of nearly 11. This result is in line with that of Slitcher et al (18). Fever has been suggested to increase platelet consumption and clearance, but fever can be confounded by other factors such as medication (35). Unexpectedly, the presence of infection was not significantly associated with platelet refractoriness. This finding is supported by other studies which did not show any apparent association between septicemia and platelet refractoriness (18,36,37). Similarly, the presence of bleeding during platelet transfusion was not significantly associated with platelet refractoriness regardless of the WHO bleeding score, thus supporting findings from previous studies (36,38). Unlike the study by Shastry et al, which showed that platelet refractoriness was significantly influenced by splenomegaly, in the present study we could not identify such an association (36). This might at least partly be due to the low proportion of patients with splenomegaly in our study compared to that of Shastry et al.

The majority of our patients had a previous history of blood transfusion, and it is known that transfusion exposes the recipients to other foreign HLA antigens and may lead to alloimmunization, thereby increases the risk of platelet refractoriness, although this is rare, as reported by Fabris et al (38). There was, however, no significant association between previous history of blood transfusion and platelet refractoriness in our study.

Furthermore, in our study, none of the patients were using heparin or amphotericin B, drugs that have previously been associated with platelet refractoriness (39-41). There were, however, a few patients who used vancomycin (that may lead to platelet refractoriness), but no significant association was found with platelet refractoriness. This correlates with the findings from Bishop et al (39).

Our separate analysis revealed that our platelet concentrates were of good quality when compared to studies in similar hospital settings in other low- and middle income countries (5,9,10). Low concentration of WBC has been of particularly importance as it reduces cytokine release from damaged WBC and thus reduces platelet alloimmunization (21).

Notably, we only controlled platelet quality after one day of storage and we thus cannot rule out a reduction of quality beyond the first day of storage.

Our study has some limitations. The presence of anti-HLA antibodies and anti-HPA antibodies were not studied since these tests were unavailable at MNH. Our recruitment procedure may have been prone to selection bias, even though in this study almost all patients who received platelets met the criteria for inclusion into the study. Also, the small number of included study patients may have impacted on our association analyses.

Conclusion

Approximately a third of all patients receiving platelet transfusion experienced platelet refractoriness and this was strongly associated with fever. Future studies of the mechanisms of development and progression of platelet refractoriness should also include examination of anti-HLA- and anti-platelet-antibodies. The quality of platelet concentrates prepared at MNH is good in terms of platelet count and residual WBC. Further studies are recommended to assess other parameters for quality of platelet concentrate which were not analysed in our study.

Competing interests

The authors declare no competing interests.

Author's contributions

KML was responsible for conception, design, acquisition of data and analysis as well as drafting the manuscript. HK, POI and CC were responsible for conception, design, interpretation of data and revising the manuscript. AN was responsible for data analysis and revising the manuscript. All authors read and approved the final version of the manuscript.

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