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Time to four-factor prothrombin complex concentrate administration decreased by presence of a 24/7 pharmacist in the emergency department

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Abstract

Study objective: The objective of this study was to determine the impact of a 24/7 pharmacist (RPh) on time from order to the administration of four-factor prothrombin concentrate complex (4F-PCC) in the emergency department (ED).

Methods: This is a retrospective study that included patients who received 4F-PCC in the ED for acute reversal of oral anticoagulation before and after the implementation of a 24/7 RPh. Patients for whom 4F-PCC was ordered between May 1, 2014 and June 30, 2015 were in the pre-RPh group and those between November 1, 2018 and December 31, 2019 were in the post-RPh group. The primary end point was time from order to administration of 4F-PCC. Time from arrival to administration of 4F-PCC was also evaluated.

Results: Of 168 patients evaluated, 100 were included in the study (n = 33 pre-RPh; n = 67 post-RPh). The majority of patients were on warfarin (97.0% pre-RPh and 73.1% post-RPh) for atrial fibrillation. Both groups included trauma and intracranial hemorrhage patients. The mean time from order to 4F-PCC administration was significantly shorter in the post-RPh group (71.2 vs 35.2 minutes, $P < .001$, 95% confidence interval [CI] [27.013-44.987]). In addition, the median time from arrival to 4F-PCC administration was also shorter in the post-RPh group (153 vs 106 minutes, $P = .033$).

Conclusions: At our institution, time from order, and from arrival, to administration of 4F-PCC for reversal of oral anticoagulation in the setting of acute bleeding events in the ED was reduced by 36 minutes after the presence of a 24/7 pharmacist.

KEYWORDS

anticoagulation, pharmacy practice, stroke

1 | INTRODUCTION

1.1 | Background

Clinical pharmacists' presence in the emergency department (ED) is increasing throughout the United States with roles in antimicrobial stewardship, medication reconciliation, rapid sequence intubation, and trauma resuscitation. Pharmacists can also play a role in anticoagulation reversal, assessing for indication, and contraindication of reversal, giving the appropriate dose, and preparing the reversal product at the bedside.

Four factor-prothrombin complex concentration (4F-PCC) can be used for the acute reversal of both vitamin K antagonists (VKA) and direct oral anticoagulants (DOAC). Administering the appropriate dose of 4F-PCC for reversal of VKA is dependent on the international normalized ratio (INR). Fixed dosing of 4F-PCC has been used, but its

safety and efficacy is not discussed by Tomaselli et al.[1] Dosing strategies for DOAC reversal are dependent on the severity of the bleed. Patients experiencing a major bleeding event (a symptomatic bleed at a critical site, a decrease of hemoglobin ≥2 g/dL or those requiring ≥2 units of packed red blood cells) require higher doses of 4F-PCC for appropriate reversal of their anticoagulation. Major bleeding events require 50 units/kg instead of 25 units/kg or a standard 2000 unit dose for all other bleeds.[1,2]

1.2 | Importance

Rapid reversal of acute hemorrhage in the setting of VKA or DOAC is vital due to the high morbidity and mortality associated with bleeding, especially in a bleeding trauma patient or an intracranial hemorrhage (ICH).[1] Since the implementation of 24/7 pharmacists in the ED at our institution, pharmacists have become integral in assessing patients who require 4F-PCC administration, and they are responsible for preparing all 4F-PCC doses at the bedside in the ED.

One retrospective study of 48 patients with ICH who received 4F-PCC for reversal of a VKA in the ED showed a decrease in time to administration, from 70 to 35 minutes, after the implementation of a pharmacist-driven protocol.[3] A more recent retrospective study of 116 patients requiring reversal with 4F-PCC for a life-threatening bleed or urgent procedure assessed the impact of a pharmacist's presence in the ED on time to administration. They determined that a pharmacist present in the ED decreased time to administration of 4F-PCC from 206 to 66 minutes. All doses of 4F-PCC were prepared in the pharmacy and delivered to the ED.[4]

1.3 | Goals of this investigation

The purpose of this study was to determine if a clinical pharmacist present in the ED 24 hours per day, 7 days per week, and tasked with preparing 4F-PCC at the bedside decreased the time to administration of reversal of acute bleeding secondary to a VKA or DOAC at our institution.

2 | METHODS

2.1 | Study design and selection of participants

This single-center retrospective chart analysis was conducted at a 548 bed, level one trauma, academic medical center. Patients were included if they presented to our institution's 68 bed ED (75 000 annual visits) requiring anticoagulation reversal with 4F-PCC. Using the electronic medical record (EMR [Cerner, North Kansas City, Missouri]), patients whom 4F-PCC was ordered between May 1, 2014 and June 30, 2015 (pre-RPh) and November 1, 2018 and December 31, 2019 (post-RPh) were reviewed by a single abstractor. Patients over 18 years old receiving oral anticoagulation therapy (warfarin, rivaroxaban, apixaban, or edoxaban) requiring rapid reversal with 4F-PCC for bleeding in the ED were included. Despite its approval by the US Food and Drug Administration for apixaban and rivaroxaban reversal, andexanet alfa is not on formulary at our institution; therefore, none of the study patients received this medication. Patients receiving dabigatran therapy were excluded due to the availability of idarucizumab for dabigatran reversal. In addition, patients meeting the following criteria were excluded: those whose first dose was administered outside the ED (ie, in the operating room [OR] or intensive care unit [ICU]), administration of 4F-PCC before arrival to our ED, reversal for procedure in absence of bleeding (emergent or scheduled), or patients with a hematologic disorder.

All data points collected were based on discrete, objective data found in the EMR. A second abstractor independently reviewed a random selection of charts totaling 10% of the study cohort to ensure data quality. If a discrepancy was identified, both abstractors reviewed and came to a consensus. If more than one discrepancy identified, an additional 10% of the total study cohort would be evaluated and the process repeated.

Before July 2015, there was no pharmacist presence in the ED at our institution. At that time, a pharmacist began working 40 hours per week. It was not until November 2018 that there was full 24/7 pharmacist coverage. Because of the phased implementation of pharmacists in the ED between July 2015 and November 2018, the timeframe for the groups was chosen to ensure pharmacists were either always absent or always present in the pre and post-RPh groups, respectively. While inclusion of the intermediate time period would provide with a larger patient population, there was no reliable way to determine retrospectively when an ED pharmacist was involved, which may have confounded our results.

Before the presence of a 24/7 ED pharmacist, when 4F-PCC orders were entered into the EMR, the nurse requested the dose from the remote surgical ICU/operating room (SICU) pharmacy. All 4F-PCC orders were verified and dispensed by the pharmacist in the SICU pharmacy. The product was delivered to the unit by a pharmacy technician or picked up by a unit nurse. An SICU pharmacist was present at all times except Friday and Saturday nights from 22:30 to 07:00. During this gap, it was the responsibility of the central pharmacist to process all 4F-PCC orders and facilitate delivery. Upon delivery to the ED, a registered nurse prepared the dose at the bedside immediately before administration.

After the addition of 24/7 ED pharmacists, all 4F-PCC orders in the ED were processed and dispensed by the ED pharmacist. The ED pharmacist is present for all traumas, strokes, and similar emergencies where verbal orders for 4F-PCC may be given. In scenarios where electronic orders are able to be utilized, the ED pharmacist receives a page whenever a 4F-PCC order is entered. While processing the order, the ED pharmacist retrieves the dose of 4F-PCC from the SICU pharmacy and then prepares the dose at the bedside immediately before administration. The 24/7 staffing model at our institution ensures there is never a lack of pharmacist presence in the emergency department. During both study periods, 4F-PCC was dispensed from the SICU pharmacy.

2.2 | End points

The primary end point was time from order entry to 4F-PCC administration. This time was defined as the order entry time in the EMR or arrival time in scenarios where verbal orders are used (eg, traumas). Arrival time was used as a surrogate for order time since time of a verbal order could not be determined retrospectively. All other order times were obtained from the electronic order in the EMR.

Secondary end points included time from arrival to the ED to administration of 4F-PCC, ICU length of stay (LOS), hospital LOS, number of transfusions, and admission mortality. Subgroup analyses were performed to evaluate the time from order entry to administration and from arrival to administration of 4F-PCC for trauma and ICH patients. Patients were included in the trauma group if they received emergent care through activation of the trauma response team. A positive result of an ICH on a head/brain computed tomography imaging was required for inclusion in the ICH group. The trauma and ICH groups were not mutually exclusive. These subgroups were selected due to the required response of the pharmacist. Pharmacists in our ED receive pages as members of the response team for all traumas and "brain attacks." The pharmacists are involved in these cases before identifying the need for anticoagulation reversal and ordering 4F-PCC. Due to the acuity of these situations, and the demand for an interprofessional response, further analysis was desired to evaluate the impact of a 24/7 pharmacist in the ED.

An additional analysis was performed to evaluate administration of intravenous (IV) phytonadione in warfarin patients for complete reversal. We hypothesized that the presence of a 24/7 pharmacist in the ED reduced the time to administration of 4F-PCC for acute reversal of oral anticoagulation.

The research protocol was submitted to the Institutional Review Board and received exemption status. Study data were collected and managed using REDCap electronic data capture tool.[5] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: (a) an intuitive interface for validated data entry; (b) audit trails for tracking data manipulation and export procedures; and (c) automated export procedures for seamless data downloads to common statistical packages, and procedures for importing data from external sources.

2.3 | Analysis

Baseline demographics were reported using descriptive statistics including mean ± SD and median (interquartile range [IQR]) as appropriate. Skewness and kurtosis were used to assess for normal distribution. Continuous, normally distributed data were evaluated with a *t*-test and non-parametric data was analyzed using a Mann-Whitney *U* test. Categorical data were evaluated using a χ^2 or Fisher's exact test as appropriate. Data were analyzed using SPSS Statistics (Version 25, IBM Corp, Armonk, New York) and Microsoft Excel (Microsoft Corporation, Redmond, Washington).

3 | RESULTS

3.1 | Characteristics of study subjects

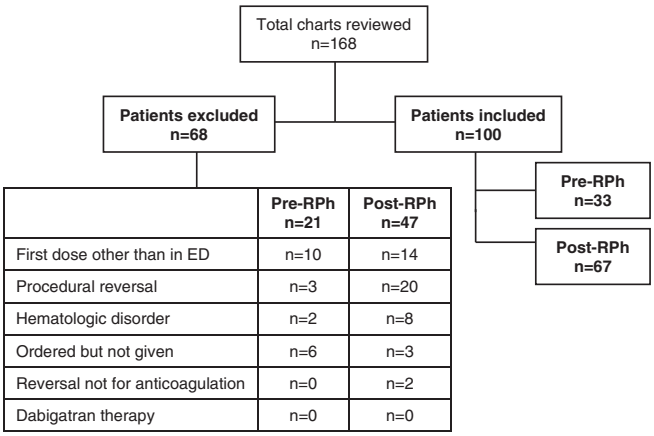
During the study period, 168 charts were reviewed regarding the administration of 4F-PCC, and 100 patients were included in the study. Of the 100 patients included, 67 patients had a 24/7 pharmacist (post-RPh) and 33 did not (pre-RPh). The most common exclusion criteria were the first dose of 4F-PCC given outside the ED for the pre-RPh group and procedural reversal in the post-RPh group (Figure 1). Baseline characteristics were collected and reported for the two groups (Table 1). A single subject could have been on more than one antiplatelet and had more than one indication for anticoagulation. There was no adjustment made for differences in baseline characteristics.

3.2 | Main results

The mean time from order entry to administration of 4F-PCC in the post-RPh group, 35.2 minutes, was significantly shorter than the pre-RPh group, 71.2 minutes ($P < .001$, 95% CI [27.0-45.0]). In addition, the median time from arrival to the ED to administration of 4F-PCC in the post-RPh group was significantly shorter than the post-RPh group ($P = .033$). Hospital LOS and ICU admission were greater in the post-RPh group. ~~A~~dmission mortality occurred at similar rates between the pre- and post-RPh groups ($P = 1.00$; Table 2).

3.3 | Subgroup analyses

Additional post-hoc analyses were performed to assess for a difference in time from order entry to administration and time from arrival to administration of 4F-PCC for patients presenting with trauma or ICH. The ICH subgroup was consistent with the findings of our



	Pre-RPh n=21	Post-RPh n=47
First dose other than in ED	n=10	n=14
Procedural reversal	n=3	n=20
Hematologic disorder	n=2	n=8
Ordered but not given	n=6	n=3
Reversal not for anticoagulation	n=0	n=2
Dabigatran therapy	n=0	n=0

FIGURE 1 Exclusion criteria. ED, emergency department; RPh, pharmacist

TABLE 1 Baseline characteristics

Baseline characteristics	Pre-RPh (n = 33)	Post-RPh (n = 67)	*P*-value
Male, n (%)	16 (48.5)	42 (62.7)	.201
Age (years), mean ± SD	75.5 ± 12.9	75.8 ± 15.1	.932
Race			
Caucasian	31 (94.0)	62 (92.5)	.335
African-American	1 (3.0)	5 (7.5)	
Other	1 (3.0)	0 (0.0)	
Weight (kg) ± SD	81.3 ± 18.1	83.8 ± 22.9	.478
Trauma, n (%)			.216
Level I[a]	0 (0)	3 (4.5)	
Level II[b]	5 (15.2)	5 (7.5)	
Level III[c]	6 (18.2)	19 (28.4)	
ICH, n (%)	23 (69.7)	35 (52.2)	.132
Indication for anticoagulation, n (%)			.917
Atrial fibrillation	23 (69.7)	46 (68.6)	
VTE within past 3 months	1 (3.0)	5 (7.5)	
History of VTE	6 (18.2)	11(16.4)	
Cerebrovascular accident	2 (6.1)	7 (10.4)	
Aortic or mitral valve replacement	3 (9.1)	4 (6.0)	
LVAD	3 (9.1)	6 (9.0)	
Other	0 (0.0)	1 (14.9)	
Anticoagulation, n (%)			.010
Apixaban	0 (0.0)	9 (13.4)	
Edoxaban	0 (0.0)	0 (0.0)	
Rivaroxaban	1 (3.0)	9 (13.4)	
Warfarin	32 (97.0)	49 (73.1)	
Concomitant antiplatelet therapy, n (%)			.267
Aspirin, n (%)	11 (33.3)	34 (50.7)	
Clopidogrel, n (%)	2 (6.1)	2 (3.0)	
4F-PCC dose (units), median (IQR)	2202 (1678.5-3217.5)	2604 (2094-3216)	.435
4F-PCC weight based dose (unit/kg), median (IQR)	27.2 (24.1-32.4)	28.7 (25.1-47.2)	.546

Abbreviations: 4F-PCC , four-factor prothrombin concentrate complex; ICH, intracranial hemorrhage; IQR, interquartile range; LVAD, left ventricular assist device; RPh, pharmacist; VTE, venous thromboembolism.

[a]Level I trauma: patients with physiologic or anatomic abnormalities that indicate serious life- or limb-threatening injury requiring immediate intervention.

[b]Level II trauma: evidence of significant injury who do not otherwise meet level I criteria.

[c]Level III trauma: patients who meet clinical criteria based on demographics (ie, age), risk factors (ie, anticoagulation), or mechanism of injury that would benefit from an expedited evaluation to determine the presence or absence of significant injury.

primary end point for times from order entry and from arrival ($P < .001$, $P = .021$; Table 2).

4 | DISCUSSION

This study demonstrates the positive impact of a 24/7 pharmacist in the ED on time from order and arrival to administration of 4F-PCC. Through the involvement of 24/7 pharmacists in the ED, time to a potentially life-saving therapy has been reduced. The pre-RPh group had a delayed administration compared with the post-RPh group. In addition, the pre-RPh group had a larger proportion of subjects excluded due to the initiation of therapy outside of the ED (eg, ICU or OR). Initiation of therapy following transfer to the ICU or OR may represent further delay in the pre-RPh group unmeasured by our end points. Conversely, a smaller proportion of patients in the post-RPh group were excluded due to initiation of therapy outside of the ED. This may explain why the post-RPh group was able to include more patients admitted to the ICU. Further studies, which is outside the scope of this project, are needed to further elucidate the reason

TABLE 2 Study end points and subgroup analyses

	Pre-RPh n = 33	Post-RPh n = 67	*P*-value	95% CI
Time (min) from order to administration of 4F-PCC, mean ± SD	71.2 ± 31.0	35.2 ± 14.4	< .001	27.0-45.0
Time (min) from arrival to administration of 4F-PCC, median (IQR)	153 (89-205)	106 (66-142)	.033	
Hospital LOS (days), median (IQR)	4.1 (2.8-5.8)	6.9 (3.6-9.8)	.017	
ICU admissions, n (%)	10 (30.3)	43 (64.2)	.003	
ICU LOS (days), median (IQR)	1.6 (0.83-3.4)	2.2 (0.79-2.9)	.745	
Admission mortality, n (%)	4 (12.1)	10 (14.9)	1.000	
FFP within 24 hours of 4F-PCC dose, n (%)	6 (18.2)	5 (7.5)	.171	
Plt within 24 hours of 4F-PCC dose, n (%)	7 (21.2)	2 (3.0)	.005	
PRBC within 24 hours of 4F-PCC dose, n (%)	5 (15.2)	21 (31.3)	.095	
Intracranial hemorrhage	Pre-RPh n = 23	Post-RPh n = 35		
Time (min) from order to administration of 4F-PCC, mean ± SD	71.6 ± 32.6	33.2 ± 13.9	<.001	26.0-50.8
Time (min) from arrival to administration of 4F-PCC, median (IQR)	124 (73-185)	80 (54-124)	.021	
Trauma	Pre-RPh n = 11	Post-RPh n = 27		
Time (min) from order to administration of 4F-PCC, mean ± SD	71.9 ± 31.9	33.7 ± 15.0	.062	22.9-53.5
Time (min) from arrival to administration of 4F-PCC, median (IQR)	117.0 (88-174)	119.0 (54-133)	.573	
Warfarin	Pre-RPh n = 32	Post-RPh n = 49		
Intravenous vitamin K administration, n (%)	25 (78.1)	44 (89.8)	.203	

Abbreviations: 4F-PCC, four-factor prothrombin complex concentrate; CI, confidence interval; FFP, fresh frozen plasma; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; Plt, platelets; PRBC, packed red blood cells; RPh, pharmacist.

for higher rates of ICU admission and longer lengths of stay in the post-RPh group. Non-emergent, procedural reversal 4F-PCC orders were excluded from the study because administration is often purposefully delayed until just before procedure. This allowed us to focus on the assessment of reversal in acute bleeding events where rapid administration is most important.

At our institution, 4F-PCC is stored in the SICU pharmacy separate from the ED for patient safety and documentation. The automated dispensing cabinets (ADC) in our ED are non-profiled, meaning any registered user can remove a medication without an active order. Keeping 4F-PCC in one of the ADC could possibly result in inappropriate doses due to lack of evaluation by a pharmacist or drug waste due to preparation without a valid order. In addition, accurate documentation of 4F-PCC often requires a small dose adjustment based on the factor IX content. Recording of lot numbers and expiration dates in the EMR is required for every 4F-PCC dose. By keeping the medication out of the ADC, this allows the pharmacist to ensure appropriate documentation occurs with every dose.

Previous retrospective reviews showed a decrease in time to 4F-PCC administration after the involvement of a pharmacist, but none of the studies were supported by 24/7 ED pharmacists with bedside preparation of 4F-PCC. Alaraj et al compared the time to administration of PCC products for oral anticoagulation reversal with and without a pharmacist's involvement as a secondary end point for a subset of their study population. Time to administration was defined similarly to our study, from initial order to start of PCC administration. They concluded that a pharmacist participation reduced the median time to PCC administration from 42 to 24 minutes; however, while there were a total of 60 patients who qualified for inclusion in this sub-analysis, it is unclear how many patients had a pharmacist involved in their care and how many did not making the result difficult to interpret. In addition, compared with our study, an ED pharmacist was only present from 1200 to 2200 each day.[6] Corio et al evaluated 48 ICH patients taking a VKA with an INR ≥2. Time from known elevated INR and confirmed ICH was used as a start time to evaluate time to 4F-PCC administration. They determined that pharmacists present in the ED from 07:30 to 23:59 each day decreased median time from order to 4F-PCC administration from 70 to 35 minutes with bedside preparation.[3] Without full 24/7 pharmacist coverage, the authors drew similar conclusions as our study. In addition, our study demonstrated that a similar, positive outcome can be obtained in the absence of ADC storage. A larger review of 116 patients assessed the impact of

pharmacists on time from ED arrival to administration of 4F-PCC, including reversal for a procedure. Pharmacists were present for predefined hours each day where they assisted in facilitation between the ED and central pharmacy (where 4F-PCC was prepared) for bedside delivery of 4F-PCC. They determined that pharmacist involvement resulted in a decrease in median time from arrival to 4F-PCC administration from 206.5 to 66.5 minutes.[4]

At our institution, trauma and unidentified patients are preregistered resulting in falsely early arrival times. In addition, bleeding is not always apparent at initial presentation, which may further increase time from arrival to administration of 4F-PCC. Due to these factors, evaluating time from order to administration was a better representation of time from bleed identification to anticoagulation reversal and a more accurate way to assess pharmacist impact.

In our study's ICH patients, the presence of a 24/7 pharmacist decreased time from order and from arrival to administration of 4F-PCC. As a comprehensive stroke (CSTK) center, our institution is compliant with the quality measures defined by The Joint Commission.[7] Use of 4F-PCC for reversal of VKAs and DOACs is in alignment with the 2015 ICH guidelines;[8] however, these guidelines do not evaluate time to administration of the reversal agent. The ischemic stroke guidelines identify a goal of 60 minutes for door to needle time for alteplase administration. Since the establishment of this goal, it has been demonstrated that pharmacists decrease time to thrombolytic administration, which increases the compliance with Joint Commission CSTK center quality measures.[9,10] The current quality measure, CSTK-04, regarding anticoagulant reversal does not address time to administration. Previous measures have tested median time goals of time to administration of anticoagulation reversal, but it did not result in favorable administration times.[7,11] Should the inclusion of such a quality measure be reconsidered, our study demonstrates 24/7 pharmacist presence may be an effective strategy to decrease time to administration of 4F-PCC in the setting of a 24/7 pharmacist. As demonstrated in previous studies, anticoagulation reversal with 4F-PCC results in quicker INR reversal, quicker time to surgery, and superior hemostasis when compared with fresh frozen plasma (FFP).[12] Quicker administration of 4F-PCC may further reduce these times; however, a larger trial would need to be performed to adequately assess for hemostasis and outcomes of faster 4F-PCC administration.

While our trauma population was not large enough to detect a difference in time from order to administration of 4F-PCC, the clinical significance remains consistent with the whole population results. The lack of difference between the groups in time from arrival to administration of 4F-PCC is likely due to the high number of level 3 traumas. Due to the lower acuity of level 3 traumas, there is not the same urgent response from the inter-disciplinary care team, which may explain the longer time to administration. To our knowledge, there are no known guidelines recommending quicker times to anticoagulation reversal in trauma patients, but clinically, a more rapid administration time may provide faster control of bleeding.

Intravenous phytonadione administration remains an area for improvement at our institution. In the post-RPh group, five patients taking warfarin did not receive IV phytonadione. Three of the five patients were transitioned to comfort care after phytonadione was ordered but before it was administered. Intravenous phytonadione remained indicated in the other two patients. This demonstrates an area of improvement for our ED pharmacists.

As a single center, retrospective study, we were unable to account for timing of verbal orders. Because of the emergent nature of anticoagulation reversal, 4F-PCC may have been ordered verbally, administered, and later documented in the EMR leading to falsely increased times to administration. When 4F-PCC was ordered during trauma resuscitation, times may have appeared longer due to use of arrival time as the order time. This was performed because orders in trauma resuscitations are verbal and time of order is not documented. Selection bias may have resulted as demonstrated by the post-RPh group having more ICU admissions and longer lengths of stay than the pre-RPh group. Lastly, our study did not assess the impact of a faster administration time on differences in hemostasis due to the lack of readily available standard of care monitoring for DOACs.

In summary, time from order, and from arrival, to administration of 4F-PCC for oral anticoagulation reversal for acute bleeding events in the ED was reduced at our institution by the presence of a 24/7 pharmacist.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors have made substantive contributions to the study, and all authors endorse the data and conclusions.

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