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Original Article

Rhabdomyolysis in Patients with Drug or Chemical Poisoning: Clinical Investigation and Implications

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What's Known

- Rhabdomyolysis, a syndrome caused by skeletal muscle injury, leads to the release of toxic intracellular contents into the bloodstream.
- Toxic agents, particularly drugs and chemicals, account for a substantial proportion of rhabdomyolysis cases, contributing to 80% of adult presentations.

What's New

- The study focused on poisoning-induced rhabdomyolysis in Yazd province, Iran, identifying the most common causes and clinical outcomes.
- Methadone emerged as the primary causative agent, showing strong associations with both acute kidney injury (AKI) requiring dialysis and increased mortality risk. While AKI necessitating dialysis served as a significant predictor of death, neither age nor sex substantially influenced these risks.
- These findings emphasized the importance of vigilant monitoring for rhabdomyolysis and AKI in poisoning cases, particularly those involving methadone, to enhance patient outcomes.

Abstract

Background: Given that poisoning patterns vary by region and no comprehensive data exist on chemical/drug-induced rhabdomyolysis in Yazd province (Iran), this investigation was conducted to assess rhabdomyolysis incidence among patients with drug or chemical poisoning.

Methods: This descriptive cross-sectional study was conducted on all patients with chemical or drug poisoning in Shah Vali (Yazd) and Shahid Beheshti (Taft) Hospitals, Iran, from March 2015 to 2020. All data were extracted from medical records.

Results: Among 7800 patients with poisoning, 788 individuals (10.1%) were diagnosed with rhabdomyolysis. The predominant drug poisoning agents causing rhabdomyolysis were methadone, with 327 cases (41.5%), and benzodiazepines, with 80 cases (10.1%). The most common chemical poisoning agent was lead, occurring in 18 cases (2.28%). Acute kidney injury (AKI) requiring dialysis and death occurred in 96 (12.2%) and 55 (7%) patients, respectively. Methadone was associated with the highest frequencies of death and AKI requiring dialysis, accounting for 23 (41.8%) and 41 (42.7%) cases, respectively. A significant relationship was found between death and AKI requiring dialysis (P=0.002).

Conclusion: The frequency of rhabdomyolysis was approximately 10%, with a 7% mortality rate among affected patients. Rhabdomyolysis was more frequently associated with drug poisoning than chemical poisoning, with methadone and benzodiazepines being the most frequently causative agents. Notably, methadone poisoning was associated with significantly higher rates of both AKI requiring dialysis and mortality. Moreover, AKI necessitating dialysis was identified as a significant predictor of mortality in these patients.

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Introduction

Rhabdomyolysis is a syndrome resulting from skeletal muscle injury,[1-3] leading to the release of potentially harmful cellular contents into the bloodstream.[4-6] Myoglobin excretion through urine is the major consequence of muscle damage, which causes acute renal failure in 15-33% of cases.[1] Its manifestations in poisoned patients vary from mild serum creatine kinase (CK) elevation to severe electrolyte imbalances and acute kidney injury (AKI) necessitating renal replacement therapy (RRT).[7-9]

Myoglobinuria, a consequence of muscle breakdown, is a significant contributor to acute renal failure (ARF), affecting 15-33% of cases. Additionally, rhabdomyolysis accounts for 5-25% of all ARF cases.

In cases of rhabdomyolysis, the risk of AKI is heightened by several factors, including hyperkalemia, hyperphosphatemia, hypocalcemia, dehydration, acidosis, sepsis, intravascular volume depletion, elevated serum myoglobin levels, and reduced myoglobin clearance.[7] Various toxicants can induce rhabdomyolysis through mechanisms, such as prolonged unconsciousness, immobility, agitation, seizures, falls, withdrawal, and hyperthermia.[7]

While the classic triad of muscle weakness, myalgia, and dark urine indicates rhabdomyolysis, observing all three symptoms simultaneously is rare.[1]

Rhabdomyolysis has a wide range of causes, including trauma, environmental factors, metabolic disorders, infections, immune disorders, and hereditary conditions. However, one significant but often underrecognized cause is drug and chemical poisoning.[7, 10] A variety of substances, including illicit drugs, prescription medications, and environmental toxins, have been implicated in its development. Drugs such as benzodiazepines, phenobarbital,[1] and statins,[11] as well as chemicals such as organophosphates, methanol, and carbon monoxide,[1] are known to induce muscle damage through various mechanisms.

Mousavi and colleagues revealed that the most common causes of rhabdomyolysis were opium use (28%), tricyclic antidepressants (14%), and benzodiazepine (14%).[1] Talaie and colleagues also found that opium was the most frequent cause of rhabdomyolysis.[12] Another study on rhabdomyolysis and ARF reported that the most frequently abused substances were alcohol (54%), heroin (24%), and parenteral temazepam (17%).[13] Amanollahi and colleagues similarly identified heroin, amphetamines, and cocaine as the substances most frequently associated with rhabdomyolysis.[14]

Identifying the etiology of rhabdomyolysis in cases of poisoning is critical, as it guides appropriate treatment strategies and helps prevent serious complications such as kidney failure. Despite known associations between poisoning and rhabdomyolysis, comprehensive data on its incidence, mechanisms, and outcomes in drug- or chemical-induced cases remain limited. This gap is particularly evident in regions where poisoning patterns are influenced by toxin availability, as well as social, economic, cultural, and religious factors.

In our country, especially in Yazd Province, no comprehensive study has yet investigated the role of chemical and drug poisoning in rhabdomyolysis. In this way, this study aimed to investigate the occurrence of rhabdomyolysis in patients with toxic substance exposure, focusing on contributing factors, clinical manifestations, and prognostic outcomes. By elucidating these relationships, we sought to enhance diagnostic and therapeutic strategies for poisoned patients at risk of rhabdomyolysis, ultimately reducing associated morbidity and mortality.

Patients and Methods

Sample Selection

This descriptive cross-sectional study analyzed all cases of chemical or drug poisoning admitted to Shah Vali Hospital (Yazd) and Shahid Beheshti Hospital (Taft), Iran, between March 2015 and 2020. The study population comprised eligible patients identified through a retrospective review of medical records. Due to the retrospective nature of data collection from existing medical records (2015-2020), obtaining individual patient consent was not feasible. The study protocol received ethical approval from the Ethics Committee of Islamic Azad University, Yazd Branch (IR.IAU.KHUISF.REC.1400.309).

Poisoning cases were confirmed through a comprehensive evaluation of the patient's history of poison or drug consumption and clinical findings, as evaluated by a specialist in clinical toxicology (clinical poisoning fellowship).

Rhabdomyolysis was defined biochemically as CK levels, reaching at least five times higher than the normal range (≥975 IU/L).[10]

AKI was identified when serum creatinine levels exceeded 2 mg/dL following initial fluid therapy without subsequent improvement.[10]

Data Collection Procedure

Trained researchers extracted comprehensive data from patient medical records, including demographic information (age and sex), clinical manifestations (such as loss of consciousness, seizures, and mortality), laboratory results (particularly CK levels, serum creatinine, and electrolyte panels), and specific toxic agents involved in each poisoning case. Special attention was given to documenting instances where AKI progressed to require dialysis.

Inclusion and Exclusion Criteria

The study population included all hospitalized poisoning cases confirmed through clinical history and specialist evaluation by a clinical toxicology fellow. Patients were excluded if

they had pre-existing conditions that could artificially elevate CK levels, including myositis, myopathy, muscular dystrophy, acute heart disease, chronic liver or kidney disease, or recent trauma. These exclusion criteria ensured the observed rhabdomyolysis cases were more likely attributable to poisoning rather than underlying conditions.

Statistical Analysis

All statistical analyses were performed using SPSS software (version 25, IBM Corp., Chicago, IL, USA). Categorical variables, including the frequency of AKI and mortality associated with different toxic agents, were compared using the Chi square test. A probability value of less than 0.05 was considered statistically significant for all analyses.

Results

This study analyzed 7800 poisoning cases, of which 788 patients (10.1%) developed rhabdomyolysis. The demographic distribution revealed a male predominance, with 546 cases (69.3%) occurring in men compared to 232 cases (29.4%) in women. Age distribution analysis showed the highest proportion of cases in young adults aged 19-30 years (247 cases, 31.3%), followed by those aged 31-40 years (176 cases, 22.3%). Other age groups included ≤7 years (34 cases, 4.3%), 8-18 years (121 cases, 15.4%), 41-50 years (111 cases, 14.1%), 51-60 years (50 cases, 6.3%), and ≥61 years (48 cases, 6.1%). One case (0.1%) had missing demographic data.

Analysis of 788 poisoning cases revealed distinct age-related patterns in substance exposure. The highest incidence of poisoning occurred among young adults aged 19-30 years (n=210, 26.6%), closely followed by those aged 31-40 years (n=142, 18.0%). Further examination of substance-specific patterns showed that among 31-40-year-olds, methadone was the predominant agent (n=79 cases), accounting for 55.6% of poisonings in this age group, followed by opium (n=12 cases, 8.5%). In contrast, among those aged 19-30 years, benzodiazepine poisoning was the most common causative agent (n=28 cases, 13.3% of this age group), followed by tramadol (n=21, 10.0%), and methamphetamine (n=11, 5.2%).

The frequency of clinical symptoms in patients with rhabdomyolysis is presented in table 1.

The frequency of rhabdomyolysis cases associated with drug and chemical poisoning is presented in table 2.

As shown in table 2, methadone poisoning accounted for the highest frequency of cases (41.5%).

Table 3 presents the frequency of mortality associated with drug and chemical poisoning agents.

As indicated in table 3, the highest frequency of death was associated with methadone exposure (41.8%).

The frequency of poisoning agents in relation to AKI leading to dialysis is presented in table 4.

Table 4 demonstrates that methadone exposure accounted for the highest number of AKI cases requiring dialysis (n=41).

Table 5 illustrates the relationship between sex and age range of patients with death and AKI leading to dialysis.

As demonstrated in table 5, no statistically significant relationship was observed between sex and mortality (P=0.94) and AKI leading to dialysis (P=0.68). Besides, there was no statistically significant relationship between age and mortality (P=0.23) and AKI leading to dialysis (P=0.58).

Table 1: The frequency of clinical symptoms in patients with poisoning

Clinical symptoms		Frequency n (%)
Loss of consciousness	Yes	620 (78.7)
	No	167 (21.2)
	Missing value	1 (0.1)
	Total	788 (100)
Seizure	Yes	121 (15.4)
	no	667 (84.6)
	Total	788 (100)
Death	Yes	55 (7)
	No	733 (93)
	Total	788 (100)
AKI leading to dialysis	Yes	96 (12.2)
	No	692 (87.8)
	Total	788 (100)

Table 2: The frequency of rhabdomyolysis resulting from drug and chemical poisoning

Drug compounds	Single drug or multiple drugs	Frequency n (%)
Methadone	Single	290 (36.8)
	Multiple-drug	327 (41.5)
Opium	Single	48 (6.1)
	Multiple drugs (Opium)	51 (6.5)
Heroin	Single	8 (1.1)
	Multiple drugs (Heroin)	10 (1.3)
Tramadol	Single	37 (4.7)
	Multiple drugs (Tramadol)	48 (6.1)
Methamphetamine	Single	23 (2.9)
	Multiple drugs (Methamphetamine)	36 (4.56)
Ethanol	Single-drug	8 (1.01)
Trazodone	Single-drug	2 (0.25)
Phenobarbital	Single-drug	4 (0. 50)
TCA	Single-drug	3 (0.38)
Propranolol	Single-drug	7 (0.88)
Minoxidil	Single-drug	1 (0.12)
Baclofen	Single-drug	7 (0.88)
Colchicine	Single-drug	1(0.12)
Clonidine	Single-drug	6 (0.76)
Metformin	Single-drug	4 (0.50)
Benzodiazepine (Chlordiazepoxide, Clonazepam, Alprazolam, Diazepam)	Single-drug	80 (10.15)
Aluminium phosphide	Single-drug	1 (0.12)
Snakebite	Single-drug	3 (0.38)
Methanol	Single-drug	10 (1.26)
Carbon monoxide (CO)	Single-drug	16 (2.03)
Lead	Single-drug	18 (2.28)
Organophosphorus compound	Single-drug	7 (0.88)
Pesticides	Single-drug	7 (0.88)
Unknown compound	Single-drug	108 (13.7)
Lithium	Single-drug	5 (0.63)
Trazodone	Single-drug	1 (0.12)
Other specified compounds and multi-drug compounds	Single-drug	17 (2.15)
Total	Single-drug	788 (100)

Table 3: The frequency of mortality associated with drug and chemical poisoning agents

Drug/chemical poisoning	Death n (%)
Methadone	23 (41.80)
Propranolol	1 (1.81)
Opium	5 (9.09)
Tramadol	6 (10.90)
Methamphetamine	2 (3.63)
Clonidine	1 (1.81)
Benzodiazepine	5 (9.09)
Snakebite	1 (1.81)
Methanol	1 (1.81)
Unknown	10 (18.18)
Total	55 (100)

The relationship between AKI leading to dialysis and death is presented in table 6.

As shown in table 6, a significant relationship was found between mortality and AKI leading to dialysis (P=0.002).

Discussion

In the present study, among 7800 patients hospitalized for poisoning, 788 (10%) cases were diagnosed with rhabdomyolysis.

Table 4: The frequency of poisoning in relation to AKI leading to dialysis

Drug poisoning	AKI leading to dialysis n (%)
Methadone	41 (42.70)
Opium	4 (4.16)
Heroin	3 (3.12)
Tramadol	5 (5.25)
Methamphetamine	3 (3.12)
Ethanol	3 (3.12)
Trazodone	1(1.04)
Clonidine	1 (1.04)
Propranolol	2 (2.08)
Benzodiazepine	14 (14.56)
Methanol	1(1.04)
Snakebite	1(1.04)
Lithium	1 (1.04)
Unknown Compounds	16 (16.65)
Total	96 (100)

Table 5: The relationship between sex and age range of patients with death and AKI leading to dialysis

Variables		Death*		P value	AKI leading dialysis*		P value
		Yes n (%)	No n (%)		Yes n (%)	No n (%)	
Sex	Man	37 (6.8)	509 (93.2)	0.94	65 (11.9)	481 (88.1)	0.68
	Woman	16 (6.9)	215 (93.1)		30 (12.9)	202 (87.1)	
Age range	≤7	4 (11.8)	30 (88.2)	0.23	4 (11.8)	30 (88.2)	0.58
	8-18	5 (4.1)	116 (95.9)		17 (14)	104 (86)	
	19-30	15 (6.1)	232 (93.9)		32 (13)	215 (87)	
	31-40	12 (6.8)	164 (93.2)		23 (13.1)	153 (86.9)	
	41-50	10 (9)	101 (91)		11 (9.9)	100 (90.1)	
	51-60	7 (14)	43 (86)		2 (3.9)	49 (96.1)	
	≥61	2 (4.2)	46 (95.8)		7 (14.6)	41 (85.4)	

*Missing value was also observed; Chi square test. P<0.05 was considered statistically significant.

Table 6: Relation between AKI leading to dialysis and death

AKI leading to dialysis	Death		P value
	Yes n (%)	No n (%)	
Yes	14 (14.6)	82 (85.4)	0.002
No	41 (5.9)	650 (94.1)	
Total	55 (7)	732 (93)	

Chi square test; P<0.05 was considered statistically significant.

These findings were in agreement with a previous study that observed 2,418 poisoned patients who were admitted to the ICU over the 7 years and reported a 9.8% prevalence of rhabdomyolysis among these cases.[7] However, the findings of the present study differed from other studies. For instance, Faraji Dana and colleagues evaluated the prevalence and complications of rhabdomyolysis in hospitalized patients due to poisoning and found a prevalence rate of 3.65%.[15] Mousavi and colleagues observed rhabdomyolysis in only 3.2% of 3555 patients with acute poisoning.[1] These discrepancies might be attributed to variations in poisoning types, patient demographics (sex and age distribution), or other population-specific factors.

Toxins induce rhabdomyolysis through various mechanisms, such as prolonged unconsciousness, immobility, agitation, falls, withdrawal, hyperthermia, and seizures.[7] In the present study, 78.7% of patients presented with loss of consciousness. Similarly, Sharif and colleagues reported that 91.4% of patients with methadone poisoning experienced loss of consciousness, underscoring its high incidence in drug-related cases.[16] Besides, Faraji Dana and colleagues identified reduced consciousness and coma as key contributors to rhabdomyolysis pathogenesis.[15]

In this study, the rate of drug poisoning leading to rhabdomyolysis was higher than that of chemical poisoning, consistent with prior research.[17] Notably, methadone emerged as the predominant causative agent, accounting for 327 rhabdomyolysis cases. These findings were consistent with Babak and colleagues' report identifying methadone as the most frequent drug leading to rhabdomyolysis.[18] This association might be attributed to the increasing use of methadone, partly due to the expansion of addiction treatment clinics in recent years.

In the present study, benzodiazepines represented the second most frequent cause of rhabdomyolysis after methadone, accounting for 80 cases (10.15%). These findings were consistent with previous research by Mousavi and colleagues, who reported that benzodiazepines as the second leading cause with a frequency of 14%.[1] Similarly, Faraji Dana and others observed, a comparable frequency of 11.2% for rhabdomyolysis in benzodiazepine-poisoned patients.[15]

In our study, opium was identified as the third most common cause of rhabdomyolysis (n=48 cases). While these findings differed somewhat from previous studies, they provided important context. Mousavi and colleagues reported opium as the most frequent cause, with 46 cases.[1] Similarly, another study found opioid overdose (including opium) to be the predominant cause, accounting for 28% of rhabdomyolysis cases.[10] Faraji Dana and colleagues also identified opium as the primary cause of rhabdomyolysis, which partially aligned with our observations.[15]

Talaie and colleagues found that opioid components, particularly opium poisoning (23.3%) were the most frequent cause of rhabdomyolysis. Benzodiazepines, phenobarbital, propranolol, aluminum phosphide, alcohol, and co-poisoning cases were reported as subsequent leading causes in their study.[12]

These findings collectively demonstrated a significant association between opioid use, particularly opium, and the development of rhabdomyolysis across multiple clinical studies.

Majidi and colleagues identified a significant correlation between tramadol overdose and rhabdomyolysis.[19] This association might reflect the increasing prevalence of tramadol use among young adults and changes in drug misuse trends in recent years. Overall, these findings underscored the critical need for enhanced clinical awareness, preventive measures, and targeted treatment strategies for opioid-related complications, particularly in light of emerging drug abuse trends.

A study that was conducted in the USA, analyzing approximately 26,000 annual rhabdomyolysis cases from the National Hospital Discharged Patients Database identified alcohol intoxication as the most prevalent etiology, followed by illicit drug use.[20] These findings demonstrated significant geographical variation in the etiological patterns of poisoning-induced rhabdomyolysis.

According to the findings of the present study, the highest frequency of rhabdomyolysis was observed among patients aged 19-30 years, followed by those aged 31-40 years. These findings were consistent with Babak and colleagues' report identifying 20-39 years as the most common age range for rhabdomyolysis (20-29 years and 30-39 years).[18] Further supporting this pattern, Faraji Dana and colleagues found a mean age of 35.5±15.49 years among rhabdomyolysis patients,[15] confirming the higher prevalence in younger populations.

These findings collectively indicated that poisoning-related rhabdomyolysis occurred more frequently among younger individuals and could result in severe complications, including progressive renal failure. Given the elevated mortality risk associated with poisoning in this population, prompt diagnosis and intervention are critical.[18] Notably, the present study identified that approximately 20% of rhabdomyolysis cases occurred in patients under 18 years old, predominantly associated with methadone use.

The increasing incidence of poisoning among young individuals appears multifactorial, potentially attributable to: (1) insufficient substance awareness, (2) accidental accessibility, (3) parental factors (negligence, addiction history), (4) improper storage practices (e.g., using beverage containers), and (5) low parental educational levels.[21] To mitigate these risks, we recommend: (1) proper storage of methadone in suitable containers, (2) keeping it out of reach of children, (3) public education about methadone's adverse effects, and (4) awareness campaigns about pediatric poisoning symptoms, and (5) targeted educational programs for parents regarding accidental childhood poisoning.[16]

The primary complication induced by rhabdomyolysis was AKI. In the present study, we observed AKI in 96 cases (12.2% of patients with rhabdomyolysis). This finding aligned with existing literature, though with some variation: Mousavi and colleagues reported rhabdomyolysis in patients with acute poisoning and observed AKI in 8.7% of patients.[10] However, Rodriguez and colleagues documented a broader AKI risk range of 13-50% in rhabdomyolysis patients.[20]

Multiple factors contribute to AKI risk in

rhabdomyolysis, including hyperkalemia, hyperphosphatemia, hypocalcemia, dehydration, acidosis, sepsis, intravascular volume depletion, and impaired myoglobin clearance.[7] While the precise mechanism of AKI in rhabdomyolysis was unknown, the proposed mechanisms include: (1) mechanical tubular damage from myoglobin precipitation, (2) direct toxic action of free chelate iron on tubules, and (3) hypovolemia. Notably, the degree of myoglobin released in the blood correlated with both serum CK levels and AKI severity.[1]

The findings of the present study demonstrated a significant association between AKI leading to dialysis and mortality. This finding contrasted with the findings of a previous study which reported that AKI necessitating in-hospital dialysis was associated with an increased risk of chronic dialysis dependence but not necessarily with all-cause mortality.[22] In contrast, Rodriguez and colleagues showed that AKI significantly elevated mortality risk in rhabdomyolysis patients, with higher in-hospital death rates observed in AKI patients than those without AKI.[20] Collectively, these studies establish AKI as a clinically significant risk factor for rhabdomyolysis outcomes.

Furthermore, the present study found a 7% mortality rate among rhabdomyolysis patients, with the highest frequency of death attributed to methadone, tramadol, and benzodiazepine poisoning, respectively. This finding differed slightly from Mousavi and colleagues' study, which reported a 4.2% mortality rate in rhabdomyolysis cases.[1] Afzali and colleagues conducted a study in Hamadan and identified organophosphorus poisoning as the leading cause of death, followed by drug-related causes.[23] Park and colleagues examined rhabdomyolysis outcomes across three groups, including pesticides, drugs, and other chemical groups, and found no significant difference in mortality rates between chemical and non-chemical groups. Moreover, they noted that some fatalities occurred as rhabdomyolysis progressed.[24]

However, the exact contribution of rhabdomyolysis to these fatalities remains unclear. The observed deaths might have resulted from the combined effects of rhabdomyolysis and pesticide poisoning, potentially acting synergistically.

This study had several limitations. First, as a medical record review, it was constrained by the availability and accuracy of documented data; missing or incomplete records might have affected the results. Second, since the research was conducted in only two hospitals within Yazd Province, the findings might not be generalizable to other regions or populations with differing poisoning patterns. Third, the lack of long-term follow-up data prevented the assessment of rhabdomyolysis' lasting effects or potential recurrence of poisoning events in survivors. Finally, we did not analyze potentially influential factors, such as exact drug dosages or precise treatment timelines, which could provide further insight into rhabdomyolysis severity and progression. These limitations should be considered when interpreting the findings and may guide future research directions.

Conclusion

The study identified that approximately 10% of patients with drug or chemical poisoning developed rhabdomyolysis, with approximately a 7% mortality rate among patients with rhabdomyolysis. Methadone and benzodiazepines emerged as the most frequent causative agents, with methadone poisoning significantly associated with higher rates of AKI leading to dialysis and mortality.

As the first comprehensive investigation of rhabdomyolysis in poisoned patients from Yazd Province, this study provided novel epidemiological data highlighting the clinical consequences of toxicant-induced rhabdomyolysis. The findings underscored the critical need for early detection and aggressive management of AKI in suspected rhabdomyolysis cases to improve outcomes. These findings could aid physicians in identifying high-risk cases and implementing timely interventions to mitigate severe complications associated with drug or chemical poisoning.

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Authors' Contribution

F. E: Study design, data analysis, and drafting and critical reviewing the manuscript; H. O: Study design, analysis, and interpretation of data for the work, and drafting the manuscript; S.Sh, N.D, H.F.D and H.Gh: Study design, critical reviewing the manuscript; F.F.A and R.H.Z: Study design, Data acquisition, data analysis, and drafting the manuscript; M.Sh: Study design, data analysis, and drafting the manuscript. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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