

A Study of Snakebite Envenomation Cases Admitted to Egyptian National Poisoning Center

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Abstract

Introduction: Snakebite is an Egyptian health problem since ancient Egypt. Meanwhile, there is still no controlled geographical and medical studies on locally prevalent snake family intoxication. **Aim and Methods:** The present study aimed to investigate local snakebites presentations, management, prognosis, and the effect of the polyvalent antivenom, locally produced by the Holding Company for Biological Products and Vaccines (VACSERA) through the year 2015. **Results:** A total of 87 snakebites caused by venomous and nonvenomous species were recorded. Most cases were middle-aged males. Most cases presented in summer and in the evening time. Two major groups of venomous Egyptian snakes were identified, Viperidae and Elapidae species, based on history, characteristic symptoms, and laboratory findings. Most snakebites (56 cases) were reported to be nonvenomous bites (64.4%). Twenty-one cases (24.1%) of snakebites were reported to be venomous bites by Elapidae snakes and 10 cases (11.5%) were reported to be venomous bites by Viperidae snakes. Antivenom was administered before referral to 37 (42.5%) of cases, and 19 only of them were victims of venomous snakes. Thirty-six (41.3%) patients received antivenom during admission including all cases of the venomous bites and 8.9% of nonvenomous bites' cases. **Conclusion:** Patients who had moderate or severe symptoms were effectively treated with VACSERA's polyvalent antivenom, with doses related to the severity grading and snake species identification. Additional antivenom doses were repeated on the bases of the clinical condition. Many snakebite victims referred from primary health centers received inadequate or nonnecessary doses of antivenom. No cases of anaphylaxis were recorded. There were no mortalities with current National Center for Clinical and Environmental Toxicology's protocol of treatment.

Keywords: Antisnake venom, Egypt, Elapidae, snakebite, Viperidae

INTRODUCTION

Venomous snakebite is a significant cause of global morbidity and mortality. Venomous snakes are found almost throughout the world. Most data suggest that they cause in excess of 3 million bites/year with >150,000 deaths, particularly in rural tropical areas.^[1] At least 421,000 cases of envenoming and 20,000 deaths occur every year worldwide due to snakebite.^[2]

There are many species of snakes prevalent in Egypt; these include Elapidae (*Naja haje* [Nh], *Naja nigricollis* [Nn], *Naja pallida*, and *Walterinnesia aegyptia* [Wa]),^[3-5] Viperidae (*Cerastes cerastes*, *Cerastes vipera*, *Pseudocerastes persicus fieldi*, *Echis pyramidum*, *Echis coloratus*, and *Echis carinatus*),^[4-6] Typhlopidae (*Ramphotyphlops braminus*), Boidae (*Eryx jaculus*), and Colubridae (*Psammodon sibilans*).^[5]

Snakebite is an ancient medical problem in Egypt. An ancient Egyptian Papyrus kept at the Brooklyn Museum in New York

illustrates a systematic description of 38 snakes and their bites with many remedies and a few spells for those bitten by snakes.^[7]

Venomous snakes mainly have hemotoxic (Viperidae) and/or neurotoxic (Elapidae) venom.^[8] Coagulopathy is a common and serious manifestation of severe Viperidae snake envenoming.^[9,10] Neurotoxic snake envenoming, mainly due to the Elapidae family, is one of the most important causes of snakebite fatality.^[11-15]

Different protocols exist to manage snakebite as suggested by the World Health Organization (WHO), Goldfrank's Toxicologic Emergencies textbook, and Haddad and

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How to cite this article: Gouda AS, Elnabarawy NA, Badawy SM. A study of snakebite envenomation cases admitted to egyptian national poisoning center. Acta Med Int 2017;4:34-40.

Access this article online

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10.4103/ami.ami_48_17

Winchester's (Haddad) Clinical Management of Poisoning and Drug Overdose textbook.^[16,17] These protocols are different from each other regarding management of the patients and even in the determination of the severity of envenomation.^[16,17]

Antisnake venom (ASV) is mostly effective when used at the appropriate dosage and indication.^[18] There is still a conflicting advice among physicians about the appropriate dosing, frequency of administration, and duration of therapy. Recommendation of a universal initial dose is a difficult issue as there is no well-known end point available in antivenom administration against envenoming snakebites.^[19,20] Furthermore, the neutralizing power of antivenoms varies according to the type of antivenom and from batch to batch.^[21] Even when the venom is neutralized by antivenom, there may be a delay before the recovery of the coagulopathy state.^[22] Evidence of envenomation is the only indication of ASV administration.^[23]

In Egypt, of three types of antivenom, only the polyvalent one is produced by VACSERA, Egypt. The polyvalent product can neutralize many Egyptian snake venoms, especially *Naja haje*, *Naja nigricolles*, *Naja pallida*, *Cerastes cerastes*, *Cerastes vipera*, *Pseudocerastes persicus fieldi*, and *Walterinnesia aegyptia*.^[4] It is produced as lyophilized powder vial accompanied by 10 ml diluent vial.^[24]

According to manufacturers' recommendations (VACSERA), the initial recommended dose of antivenom is 3–5 vials, intravenous infusion over 1 h. Additional antivenom doses may be repeated on the basis of the clinical condition. Although dosing recommendations are vague, up to 10 vials can be administered.^[24] Coral snakes need less doses.^[16] In general, total dose required is the amount needed to neutralize venom and cease symptoms.^[24]

Inadequate knowledge of first aid measures and the definitive therapy has led to so much mortality.^[25] Differences in victim demographics, clinical effects, managements, and outcomes among native Viperidae and Elapidae species have not been systematically characterized. The epidemiological features of snakebite are inadequate in most countries.^[26] The true impact of snakebite is also very likely to be underestimated, and reliable information on its incidence, morbidity, and mortality is limited worldwide.^[2,27,28] The aim of this work is to study demographics, prevalence and clinical effects, evaluate managements, and outcomes among native Viperidae and Elapidae species victims. Furthermore, it is extended to evaluate the current protocol of snakebite treatment at National Center for Clinical and Environmental Toxicology (NECTR).

MATERIALS AND METHODS

A cross-sectional study was conducted on all cases of snakebite victim cases admitted to (NECTR), Cairo University, during the year 2015. NECTR is a national poisoning control center located in Kasralainy Teaching Hospital, Cairo University. The study included the patients referred from other hospitals

in Egypt or presented directly at the NECTR's emergency department which has the facilities for managing snakebite cases.

Data were collected from their medical records including history and clinical examinations, investigations performed, treatment administered, and outcome. Data collected covered the period from January 1, 2015, to December 31, 2015. All snakebite cases with or without signs of envenomation were included for the study. The data collected included various information on patient demographics, age, gender, month and time of admission, suspected species of the snake, local and systemic signs and symptoms, laboratory findings, length of stays, and hospital treatments including antivenom therapy.

Inclusion criteria were all cases with recent isolated snakebite injury with delay <24 h period. Exclusion criteria are cases with no confirmative history of snakebite, cases with delay >24 h period, and cases with medical history of bleeding tendency, neurological disease, or chronic debilitating disease.

Identification of species is difficult by the layperson, and its description by the victim is often misleading because the incident is mostly accidental. The physicians in NECTR rely on the clinical features and laboratory findings of envenoming to infer the biting species. The reported snake species were classified into venomous and nonvenomous species based on toxicity and symptomatic identification. The counting of nonvenomous bites also included dry bites of unknown species.

Attempts of biting species detection were based on clinical effects of envenoming as the presence of pain, anxiety, ptosis, descending paralysis, abnormal coagulation, local edema, or respiratory arrest.

A clinical-laboratory severity grading scale used in the study for classification of envenomation severity:^[29,30]

- Grade 0 – no envenomation
- Grade 1 – minimal envenomation (local swelling and pain without progression)
- Grade 2 – moderate envenomation (swelling, pain, or ecchymosis progressing beyond the site of injury, mild systemic, or laboratory manifestations)
- Grade 3 – severe envenomation (marked local response, severe systemic findings, and significant alteration in laboratory findings).

Investigations were carried out routinely and repeated each 4–6 h in symptomatic cases, including hemoglobin level, white blood cells, prothrombin time, and international normalized ratio (INR).

On admission to the hospital, all snakebites cases had their wound cared and the injured extremity was immobilized in a padded splint in near full extension and elevated above the level of the heart to avoid dependent edema. Symptomatic and supportive treatment consisted of intravenous fluids, analgesic, anxiolytic, and antibiotics. Hydrocortisone and chlorpheniramine were administered in most of symptomatic cases.

All symptomatic cases started their antivenom therapy, and polyvalent lyophilized powder antivenom serum vials produced by VACSERA, Egypt.^[24] Doses were administered according to manufacturer's recommendations as 5–10 vials as initial dose by slow intravenous infusion after dilution with normal saline at a rate of 5–10 ml/kg body weight over 1 h. A further dose of five vials of antiserum had been administered if signs and symptoms of toxicity persist until improvement of symptoms. Cases suspected with Elapidae snakebites needed lower doses as three ampoules for initial and maintenance doses. Doses administered till neutralization of venom and cessation of all symptoms.^[24]

Statistical analysis and display of collected data had been done by the use of Excel, Microsoft Office 2013 spreadsheet software. The study followed the principles of the Declaration of Helsinki, ethical principles for medical research involving human subjects.

RESULTS

A total of 87 snakebites caused by venomous and nonvenomous species were recorded from January 1 to December 31, 2015, in NECTR. The snakebites were more common during the summer; sixty-five (75%) cases were reported during the summer months from May to October. The monthly distribution of snakebites is demonstrated in Figure 1. The highest incidence happened in the evening from 4:00 PM to 12:00 AM [Table 1].

All snakebite patients' ages ranged (2–64 years) with a median age of 30.4 years. Males were more prevalent than females irrespective of venomous or nonvenomous status. The sex distribution was 24 females (27.58%) and 63 males (73.41%). The male-to-female ratio was 2.66: 1.

Cases came from Cairo and eight cities: Alexandria, Aswan, Beni suef, Faiyum, Giza, Qalyubia, Kena, and Sinai. The ratio of cases per geographic region is presented in Figure 2. Giza, Fayoum, and Beni suef cities were the origin of most of the envenomations and accounted for almost 74% of all cases.

The clinical symptoms and signs were shown in Table 1. Symptoms of pain, local edema, anxiety, bluish discoloration, ptosis, respiratory arrest, and abnormal coagulation were the most frequent local and systematic symptoms of snakebites.

Seventy-one patients (82%) presented with anxiety, 32 patients (37%) presented with local symptoms of pain, 16 patients (18.4%) presented with ptosis, 15 patients (17%) presented with local edema, 14 patients (16%) presented with descending paralysis, 9 patients (10.3%) presented with respiratory arrest, and 3 patients (3.4%) presented with bluish discoloration. Ten patients (11.5%) had an abnormal

Table 1: Clinical features of 87 Egyptian patients with snakebites

Characteristics	Data
Age (year)	2-64
Gender, male/female	63/24
Average duration of hospital stay (day)	
Venomous	2
Nonvenomous	0.53
Discharge against medical advice	20 (23)
Admission time (%)	
12 AM to 08 AM	18 (20.7)
08 AM to 4 PM	24 (27.6)
04 PM to 12 PM	43 (49.4)
Unknown	2 (2.3)
Type of snakes (%)	
Elapidae	21 (24.1)
Viperidae	10 (11.5)
Nonvenomous	56 (64.4)
Signs/symptoms (%)	
Pain	32 (37)
Anxiety	71 (82)
Nonsystematic symptoms	56 (64.4)
Local manifestations	
Local edema	15 (17)
Bluish discoloration	3 (3.4)
Neurotoxic manifestations	
Ptosis	16 (18.4)
Respiratory arrest	9 (10.3)
Descending paralysis	14 (16)
Coagulopathic manifestations	
Abnormal coagulation	10 (11.5)
Treatment (%)	
Antivenom before referral to hospital	37 (42.5)
Antivenom during admission	36 (41.4)
Mortality	None

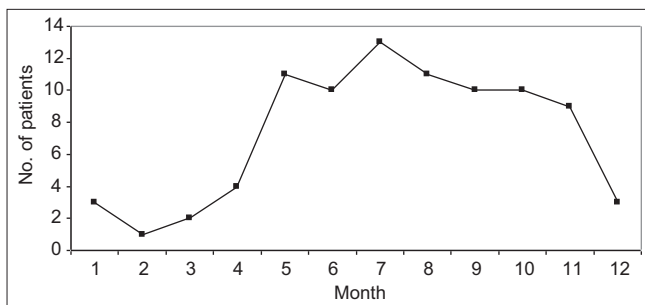


Figure 1: Distribution of snakebite patients according to season

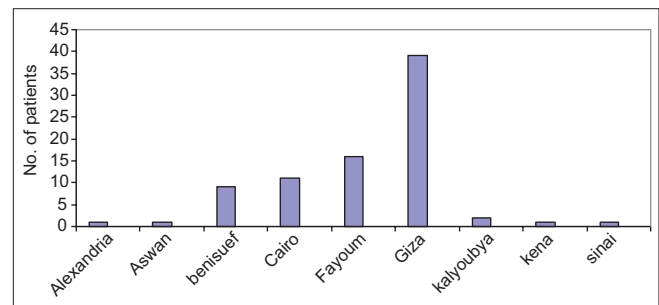


Figure 2: Geographic distribution of snakebite patients

coagulation profile with the average INR of 11.261 and standard deviation of 7.97.

Snake species were classified into three main categories based on clinical and laboratory findings [Table 2]: (a) most snakebites, 56 of 87 cases (64.4%), were reported to be nonvenomous bites by nonvenomous species or dry bites, (b) twenty-one of 87 cases (24.13%) of snakebites were reported as venomous bites by Elapidae snakes (the cases presented with paralysis), and (c) ten of 87 cases (11.49%) were reported as venomous bites by Viperidae snakes (the cases presented with abnormal coagulation).

Patients were graded according to the severity criteria as shown in Table 3. Majority of the patients had Grade 0 (48.3%) followed by grade severe (24.1%), grade minor (13.8%), and grade moderate (11.5%).

Antivenom was administered to 51 of 87 (59%) of patients including administration before referral to hospital [Tables 1 and 4]. Before referral, 37 cases (42.5%) were administered antivenom. Eighteen (32.1%) of these cases were nonvenomous. Eleven cases (52.4%) were Elapidae victims and 8 cases (80%) were Elapidae victims.

Doses of antivenom before referral mostly were one ampoule (16 cases of which 11 were nonvenomous, 3 were Elapidae, and 2 were Viperidae). Two ampoules (11 cases of which 2 were nonvenomous, 6 were Elapidae, and 3 were Viperidae). Three ampoules (6 cases of which 3 were nonvenomous, 1 was Elapidae, and 2 were Viperidae). Four ampoules (2 cases of which 1 was nonvenomous and 1 was Elapidae). One case of Viperidae administered 10 ampoules before referral. One of the nonvenomous snakebite cases administered scorpion antivenom together with the snake antivenom before referral.

During admission, none of the Grade 0 patients (0 of 42) received antivenom. Five of 14 (35.7%) of Grade 1 cases received antivenom. Nearly 100% of Grade 2 and Grade 3

received antivenom. Antivenom was used mostly in patients in whom the benefits of treatment are considered to exceed the risks of antivenom reactions. Indications for antivenom include signs of systemic and/or severe local envenoming. Thirty-six patients received antivenom during admission; 31 of 31 (100%) venomous bites and 5 of 56 (8.9%) nonvenomous bites.

The median hospital stays for snakebite cases of venomous and nonvenomous bites were 2 days and 0.53 day, respectively. Twenty of 87 (23%) patients were discharged against medical advice. No adverse reactions for the antivenom were observed with the reported cases. Re-admissions and/or mortality were not reported.

DISCUSSION

Most patients were typically males with a median age of 30.4 years due to more exposure of male to fieldwork. Most of cases of snakebite occur during summer season (May–October) and particularly in the evening similar to other studies.^[31,32] Worldwide, snakebites occur most frequently in the summer season when humans are outdoors and snakes are active as they come out of their shelters.^[2,33,34] Rural regions reported more snakebites (74%) than anywhere else because of more intense agricultural activities consistent with previous reports.^[2,28,34,35]

Most cases showed no clinical manifestations for envenomation. Bites by nonvenomous snakes are common and bites by venomous species are not always accompanied by the injection of venom (dry bites).^[36] No systemic symptoms are characteristics of nonvenomous species. Most patients (82%) had anxiety symptoms even if they are not bitten by venomous species. Most people believe that any bite from any snake will result in envenomation; however, 64.4% of all snakebites in this study did not result envenomation.

Descending paralysis, ptosis, and respiratory arrest were the most common snakebite neurotoxic syndrome attributed to bites of Elapidae species [Table 2]. Neurotoxicity is a well-known

Table 2: Clinical symptoms of envenomation

Type of snakes	Pain	Anxiety	Ptosis	Descending paralysis	Abnormal coagulation	Local edema	Respiratory arrest	Number of patients receiving antivenom (%)
Elapidae	+/-	+/-	+/-	+	-	+/-	+/-	21 of 21 (100)
Viperidae	+	+	-	-	+	+	-	10 of 10 (100)
Nonvenomous	+/-	+/-	-	-	-	+/-	-	5 of 56 (8.9)

+/- refers to presence/absence of symptom

Table 3: Grades of envenomation

Grade	Severity	Symptoms	Number of patients (%)	Number of patients receiving antivenom (%)
0	Dry bite	Minimal pain, no systematic symptoms	42 (48.3)	0 of 42 (0)
1	Minor	History of immediate pain, local edema, no systematic symptoms	14 (16.1)	5 of 14 (35.7)
2	Moderate	History of immediate severe pain, moderate systematic symptoms, intravascular coagulation	10 (11.5)	10 of 10 (100)
3	Major	History of immediate severe pain, severe systematic symptoms, intravascular coagulation, or paralysis	21 (24.1)	21 of 21 (100)

Table 4: Cases who administered antivenom before referral

Group	Cases administered with antivenom before referral (number of ampoules)						1 anti- scorpion venom	Total
	0	1	2	3	4	10		
Elapidae	10	3	6	1	1			21
Nontoxic	38	12	2	3	1		1	57
Viperidae	2	2	3	2		1		10
Grand total	50	17	11	6	2	1	1	88

feature of envenoming due to Elapidae family.^[37] Snake venoms can act as both presynaptic and postsynaptic neurotoxins at the neuromuscular junction and can induce weakness and paralysis. Neurotoxic envenoming causes a progressive descending flaccid paralysis. Ptosis is usually the first sign, then facial and bulbar involvement progressing to paralysis of the respiratory muscles and peripheral weakness in severe cases.^[38] Nine patients (10.3%) presented with neurotoxic respiratory arrest due to paralysis of the respiratory muscles, which required endotracheal intubation, ventilatory support, and early antivenom treatment. These effects may be due to delay of case presentation to NECTR or ineffective first aid treatment with sufficient antivenom at the referring medical center.

Coagulopathy was a common snakebite complication attributed to Viperidae species (11.5%). The venom leads to consumption of major coagulation factors including fibrinogen, resulting in a defibrination coagulopathy.^[38] Once the venom enters the blood, it activates prothrombin continuously, formation ensues, and fibrinolysis is activated, resulting in hypofibrinogenemia and increased levels of fibrinogen degradation products.^[39] Evidence of anticoagulant coagulopathy is a useful marker of envenoming and a major indication for commencing antivenom.^[40] Anticoagulant coagulopathy is rapidly reversed with antivenom.^[41]

A grading system can be used to classify the injury and determine appropriate management [Table 3]. Most of snakebite cases, i.e., 48.3% were clinically classified as dry bite or nontoxic. Whereas 13.8% of the envenomation cases were classified as minor, 11.5% were moderate, and 24.1% were considered severe. The snakebite severity score was precise and proved to be effective.^[2] Patients who had moderate or severe systematic symptoms (Grade III and IV) or any degree of envenomation with progression of the envenomation syndrome were eligible for therapy with antivenom. Venomous snakebite diagnosis based on clinical effects of envenoming [Table 2] and laboratory finding was a useful diagnostic test to confirm which of the major snake groups are responsible for the envenoming and determine the appropriate antivenom to be administered.

The average duration of hospital stay of nonvenomous snakebites is 0.53 day and venomous snakebites is 2 day [Table 1]. Severity grade was found to be in direct proportional relation with the duration of hospital stay^[42] as symptomatic cases needed prolonged follow-up after resolution of symptoms fearing risk of recurrence.^[21] The patient was discharged after

6 h of observation if there was no local or systemic symptoms, and laboratory tests were normal.^[43] The patient was discharged after 24 h for fear of recurrence, especially in patient with initial coagulopathy.

Additional antivenom doses were repeated on the basis of the clinical observation to neutralize venom and cease symptoms. Most of the patients received antivenom (20 of 36) responds to single dosage during hospitalization. In two cases (one case with paralysis and other with coagulopathy), third dose was needed as they did not show any improvement after the first and second doses.

No mortalities were recorded in studied cases as other studies with a similar sample size, where no mortality was reported.^[44,45] All patients were survived after effective management. Thirty-seven patients received antivenom before referral to hospital; 19 of 31 (61.3%) nonvenomous bites and 18 of 56 (32%) nonvenomous bites. The data revealed that most snakebite victims presenting at primary health centers received inadequate doses of antivenom. This is mostly because many physicians at primary health centers were unable to recognize systemic signs of envenoming. Moreover, there are deficient local guidelines for first aid management of snakebites cases.^[12]

Antivenom was administered to 59% hospitalized patients including administration before referral to hospital. Thirty-six patients received antivenom during admission; 31 of 31 (100%) venomous bites and 5 of 56 (8.9%) nonvenomous bites. Administration of antivenom to nonvenomous snakebite is not recommended as it is expensive and may be associated with allergic reactions. There is a tendency among physicians to use too small doses of ASV over high doses for the treatment of cases of severe snake envenoming, to avoid the appearance of allergic reactions compared to the high doses.^[46]

Although it is reported that the use of corticosteroids or antihistamines in patients not receiving antivenom is likely of little efficacy for the reduction of swelling or inflammation in literature,^[47] these medications were described in the current study. Hydrocortisone and antihistamine (chlorpheniramine) were given for most of the cases; 85.7% of nonvenomous bites and 100% of venomous bites. Hydrocortisone was actively given intravenously in doses 1–2 g to prevent systemic anaphylactic effects.^[48] Antivenom is liable to cause severe adverse reactions including anaphylaxis. Chlorpheniramine was commonly administered with hydrocortisone to prevent early adverse reactions to antivenom.^[49,50]

The median hospital stay for snakebite cases of venomous bites is 2 day, which go in accordance with other studies.^[51] Whereas others support close daily observation for minimum 3–4 days in envenomed victims.^[52,53] The median hospital stay for snakebite cases of nonvenomous species is 0.53 day. The protocol used for management of the present study follows Goldfrank's protocol for dry bites of coral snake poisoning^[43] and drug overdose protocol.^[54] This does not follow the 2010 WHO African guidelines.^[55]

Limitations

The retrospective nature of the study was definitely a limitation of the current study. In addition, there was no follow-up data after patient discharge to monitor late complications of antivenom, and there was no documented data for NECTR's toxicological emergency hotline consultations to other health-care facilities.

CONCLUSION

Most of the patients were males. Most snakebites occur during summer, particularly in the evening. Two major groups of venomous Egyptian snakes were identified as Viperidae and Elapidae species based on characteristic systematic symptoms and laboratory findings. Descending paralysis, ptosis, and respiratory arrest were the most common snakebite neurotoxic syndrome attributed to bites of Elapidae species. Coagulopathy was the common snakebite complications attributed to Viperidae species. Patients had moderate or severe systematic symptoms effectively treated with VACSERA's polyvalent antivenom with doses subject to the severity grading and snake species identification. Additional antivenom doses may be repeated on the basis of the clinical condition. Combining of chlorpheniramine antihistamine and hydrocortisone was administered for prevention the appearance of allergic adverse reaction of the antivenom serum. Many snakebite victims referred from primary health centers received inadequate or nonnecessary doses of antivenom. There were no mortalities with current NECTR's protocol of treatment.

RECOMMENDATION

1. Demographic studies for the different types of snakes and clinical manifestation should be done in all Egyptian region
2. Physicians in rural and first aid centers must be oriented and well trained on snakebite diagnosis and treatment
3. Prophylactic corticosteroids and antihistamines is highly recommended with polyvalent antivenom
4. Setting a snakebite treatment protocol should be generalized in the ministry of health, emergency departments, and caregivers.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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