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Original Research Article

Burden and Clinical Outcomes of Clostridioides Difficile Infection among Recipients of Chimeric Antigen Receptor T-Cell Therapy in the United States: A Retrospective Study

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Abstract: ***Background*:** Chimeric Antigen Receptor T-cell (CAR-T) therapy, developed to address malignancies evading the immune system, has shown remarkable efficacy. However, its impact on infectious complications, particularly Clostridioides difficile infection, lacks real-world evidence. Our study aims to fill this knowledge gap by exploring prevalence, mortality rates, associated risk factors, and outcomes of C. difficile infections in CAR-T therapy patients. ***Methods*:** This retrospective analysis utilized National Inpatient Sample (NIS) data (2017-2019). We applied ICD-10 CM codes to identify CAR T therapy-related hospitalizations and Clostridioides difficile cases. Outcomes of interest included in-hospital mortality, length of hospitalization, total charges, and complications, associations, and interventions. Statistical analyses involved univariate and multivariate assessments, incorporating potential confounders such as age, gender, and Charlson Comorbidity Index score. Proportions and continuous variables were compared using appropriate tests with a significance level of $P < 0.05$. We conducted our statistical analysis using STATA Version 17 (College Station, TX: Stata Corp LLC). ***Results*:** We identified 685 inpatient cases of CAR-T therapy, among which 33 developed C. difficile infection, indicating an incidence of 4.8%. Mortality in the C. difficile group was 18.2%, significantly higher than the 2.8% in the non-C. difficile group (adjusted odds ratio: 7.67, 95% CI: 2.30 to 25.62, P<0.01). The mean length of stay for C. difficile cases was 30.9 days, compared to 19.1 days without C. difficile (coefficient: 11.01 days, 95% CI: 3.63 to 18.40, P<0.01). Total hospital charges were higher in the C. difficile group ($1,148,749) than the non-C. difficile group ($862,724), but not statistically significant (coefficient: $252,066, 95% CI: -78,332 to 582,464, P=0.134). Risks and outcomes associated with C. difficile included higher rates of pneumonia (aOR: 2.91, P = 0.046) and sepsis (aOR: 4.64, P<0.01) compared to those without C. difficile. Other outcomes, such as Urinary tract infection (UTI), vasopressor support, acute respiratory failure, intubation/mechanical ventilation, GI

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bleeding, Acute Kidney Injury (AKI), Acute Cerebrovascular Accident (CVA), acute liver injury, Acute Myocardial Infarction (MI), and Congestive Heart Failure (CHF), showed no significant differences between the two groups. ***Conclusion*:** This study reveals a substantial impact of C. difficile infections on CAR-T therapy patients, with elevated mortality rates and healthcare resource utilization. While providing critical insights, future prospective studies are crucial to comprehensively guide prevention and management strategies, contributing to optimal CAR-T therapy patient care.

Keywords: CAR-T Therapy, Clostridioides Difficile Infection, Mortality Rate, Infectious Complications, C. Difficile, Chimeric Antigen Receptor T-Cell Therapy.

INTRODUCTION

It was first recognized in 1909 by Paul Ehrlich that our immune system normally prevents the formation of carcinomas. Malignant neoplasms evade our immune system by downregulating major histocompatibility complex (MHC) molecules, preventing recognition by cytotoxic T lymphocytes [1]. Based on this knowledge, CAR-T therapy is developed. Chimeric Antigen Receptor T cells are lymphocytes that are genetically modified to specifically target tumor cell antigens [2]. CAR-T cell therapy has shown remarkable responses in the treatment of refractory B cell acute lymphoblastic leukemia and is now approved for diffuse large B cell lymphoma, acute lymphoblastic leukemia, mantle cell lymphoma, and multiple myeloma [1]. Besides its potential to treat malignancies, it can cause unique toxicities through its effect on the immune system, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) [3]. Prior to receiving CAR-T therapy, patients are treated with lymphodepletion agents like fludarabine and cyclophosphamide; such therapy causes cytopenia, B cell depletion, and hypogammaglobulinemia that make patients highly susceptible to infections [4, 5]. Moreover, treatment with corticosteroids and tocilizumab, an interleukin 6 receptor monoclonal antibody for CRS and ICANS, further increases the risk of infection in these patients [6]. As we recognize the infectious complications of CAR-T therapy, there is still a lack of real-world evidence regarding Clostridioides difficile infections in this subset of patients. Our study is intended to fill this gap in understanding prevalence, mortality rates, the association of other risk factors, and outcomes of C. difficile infections in CAR-T therapy patients.

METHOD

Conducted as a retrospective analysis, this study utilized data from the National Inpatient Sample (NIS), a component of the Health Care Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ) [7]. The NIS database stands as the largest publicly available all-payer inpatient care database in the United States, representing an approximately 20% stratified sample of discharges from nearly 1000 U.S. hospitals across all 50 states. It encompasses up to 30 discharge diagnoses and 15 procedural codes for each admission, recording patient demographics, insurance status, total cost of hospitalization, length of stay, and patient outcomes.

Our study focused on the National Inpatient Sample (NIS) database spanning the years 2017 to 2019, covering hospitalizations from January 1, 2017, to December 31, 2019, with records of over 18 million hospital stays.. It is essential to acknowledge that the HCUP-NIS provides comprehensive information for each admission or hospitalization but does not track individual patients. Additionally, due to the deidentified nature of NIS data, this study was exempt from requiring Institutional Review Board (IRB) approval.

Study Population

Using the International Classification of Disease, Tenth Edition, Clinical Modification (ICD-10 CM) codes, we identified hospitalizations in which CAR T therapy was designated as either the primary or secondary diagnosis. Our inclusion criteria only included patients aged 18 years and older. Following this, we classified these hospitalizations into two distinct groups: those with Clostridioides difficile infection and those without. Notably, we excluded categories such as "No charge," "Other," and "Missing value" for the primary payer (Insurance status). For CAR T-related hospitalizations, we applied the ICD-10 procedure codes XW033C3 and XW043C3. In the case of Clostridioides difficile instances, we utilized the ICD-10 Codes A047, A0471, and A0472.

Outcomes of Interest

Our primary outcomes of interest involved in-hospital mortality, length of hospitalization, and the total charges during the hospital stay. Regarding secondary outcomes, our focus was on exploring risks and outcomes associated with C. difficile

infection. To assess mortality, we used the NIS variable "DIED," while the length of hospital stays was determined using the NIS variable "LOS." Total hospitalization charges were calculated using the variable "TOTCHG." Additionally, in our examination of complications, associations, and interventions, we referred to the relevant ICD-10 codes presented in the Supplemental Table.

Statistical Analysis

In this retrospective study, we carried out a thorough analysis following the guidelines outlined by the Healthcare Cost and Utilization Project regulations, incorporating appropriate stratification, clustering, and weighted samples [8]. Our calculations involved determining odds ratios for dichotomous variables and coefficients for continuous variables. To establish a multivariate analysis model, we included various potential confounding variables, such as age, gender, race, income quartile (determined by zip code), hospital region, hospital teaching status, hospital division, hospital bed size, insurance status, and the Charlson Comorbidity Index score. The Charlson Comorbidity Index score encompasses a range of conditions associated with elevated mortality rates, including myocardial infarction, congestive heart failure, peripheral arterial disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes, hemiplegia or paraplegia, chronic kidney disease, diabetes with end-organ damage, solid tumors, leukemia, lymphoma, and AIDS/HIV [9].

Initially, we conducted univariate analyses for each of the mentioned factors to determine unadjusted odds ratios. Subsequently, in our multivariable analysis, we included only variables that showed an association with the outcome of interest based on univariable analysis (with a significance level of $P < 0.1$). For categorical variables, proportions were compared using the Fisher exact test, while continuous variables were compared using the Student t-test. All P-values were two-sided, with the threshold for statistical significance set at $P < 0.05$. Our statistical analysis was carried out using STATA Version 17 (College Station, TX: Stata Corp LLC).

RESULTS

We identified 685 inpatient cases undergoing CAR-T therapy. Among these, 33 had C. difficile infection, while 652 did not. Table 1 displays the baseline characteristics of CAR-T-related hospitalizations, categorized into those with and without C. difficile. Characteristics such as mean age, sex, race, median household income, insurance status, Charlson Comorbidity Index score, admission type, census division, and hospital bed-size are presented along with corresponding p-values in Table 1.

Table 1: Baseline characteristics of CAR T hospitalizations

	With C. difficile	Without C. difficile	Total CAR-T hospitalizations	P value
Number of hospitalizations	33	652	685	
Mean Age	58.7 years	57.1 years	57.1 years	
Sex				P = 0.298
Male	21 (66.67%)	373 (57.36%)	395 (57.81%)	
Female	10 (33.33%)	278 (42.64%)	289 (42.19%)	
Race				P = 0.080
White	23 (71.88%)	460 (70.69%)	484 (70.75%)	
Black	1 (3.13%)	33 (5.15%)	34 (5.05%)	
Hispanic	2 (6.25%)	79 (12.24%)	81 (11.94%)	
Asian or Pacific Islander	0	31 (4.83%)	31 (4.59%)	
Native American	0	5 (0.81%)	5 (0.77%)	
Other	6 (18.75%)	40 (6.28%)	47 (6.89%)	
Median household income				P = 0.758
0-25th percentile	6 (18.75%)	111 (17.07%)	117 (17.15%)	
26th to 50th percentile	8 (25.0%)	136 (20.93%)	144 (21.13%)	
51st to 75th percentile	7 (21.88%)	196 (30.11%)	203 (29.71%)	
76th to 100th percentile	11 (34.38%)	207 (31.88%)	219 (32.01%)	
Insurance status				P = 0.775
Medicare	8 (25.81%)	208 (32.01%)	217 (31.72%)	
Medicaid	2 (6.45%)	58 (9.03%)	61 (8.91%)	
Private insurance	21 (64.52%)	357 (54.83%)	378 (55.29%)	
No insurance	4 (3.23%)	26 (4.12%)	28 (4.08%)	

Charlson Comorbidity index score				P = 0.974
0	0	2 (0.31%)	2 (0.29%)	
1	0	1 (0.15%)	1 (0.15%)	
2	18 (54.55%)	369 (56.6%)	38 (5.65%)	
3 or more	14 (45.45%)	279 (42.94%)	295 (43.07%)	
Admission type				P = 0.107
Non elective	13 (39.39%)	175 (26.84%)	188 (27.45%)	
Elective	20 (60.61%)	477 (73.16%)	497 (72.55%)	
Census Division				P = 0.499
New England	2 (6.06%)	65 (10.12%)	68 (9.93%)	
Middle Atlantic	8 (24.24%)	116 (17.94%)	125 (18.25%)	
East North Central	8 (24.24%)	83 (12.88%)	92 (13.43%)	
West North Central	4 (12.12%)	48 (7.36%)	51 (7.59%)	
South Atlantic	2 (6.06%)	98 (15.03%)	100 (14.6%)	
East South Central	1 (3.03%)	17 (2.61%)	18 (2.63%)	
West South Central	4 (12.12%)	64 (9.82%)	68 (9.93%)	
Mountain	1 (3.03%)	27 (4.14%)	28 (4.09%)	
Pacific	3 (9.09%)	130 (20.09%)	133 (19.56%)	
Hospital Bed-Size				P = 0.172
Small	1 (3.03%)	93 (14.26%)	93 (13.72%)	
Medium	4 (12.12%)	86 (13.19%)	90 (13.14%)	
Large	28 (84.85%)	473 (72.55%)	501 (73.14%)	
Hospital Location/Teaching Status				P = 0.807
Rural	0	0	0	
Urban nonteaching	0	7 (1.07%)	7 (1.02%)	
Urban teaching	33 (100%)	645 (98.93%)	678 (98.98%)	

Table 2 illustrates a comparison of mortality, length of stay, and total hospital charges between CAR T-related hospitalizations with and without C. difficile. The mortality rate in the C. difficile group was 18.2%, compared to 2.8% in the group without C. difficile, with an adjusted odds ratio of 7.67 (95% CI: 2.30 to 25.62, P<0.01). Regarding the mean length of stay, the C. difficile group had a mean length of stay of 30.9 days, while the group without C. difficile had a mean of 19.1 days, indicating a coefficient of 11.01 days (95% CI: 3.63 to 18.40, P<0.01). In terms of mean total hospital charges, the C. difficile group incurred $1,148,749, whereas the group without C. difficile had charges of $862,724, resulting in a coefficient of $252,066 (95% CI: -78,332 to 582,464, P=0.134).

Table 2: Mortality, length of stay and total hospital charges

	With C. difficile	**Without C. difficile**	**Unadjusted odds ratio/Coefficient (Univariable analysis)**	**Adjusted odds ratio(aOR)/Coefficient (Multivariable analysis)**
Mortality	6/33 (18.2%)	18/652 (2.8%)	7.83 (95% CI: 3.18 to 19.25, P<0.01)	7.67 (95% CI: 2.30 to 25.62, **P<0.01**)
Mean Length of Stay	30.9 days	19.1 days	11.71 days (95% CI: 4.15 to 19.3, P<0.01)	11.01 days (95% CI: 3.63 to 18.40, **P<0.01**)
Mean Total Hospital Charges	$1,148,749	$ 862,724	$ 286,024 (95% CI: -56, 965 to 629,014, P=0.101)	$ 252,066 (95% CI: -78,332 to 582,464, P=0.134)

Table 3 displays the risks and outcomes associated with C. difficile, comparing occurrences with and without C. difficile. Pneumonia was observed in 21.2% with C. difficile and 8.7% without C. difficile, with an adjusted odds ratio (aOR) of 2.91 (95% CI: 1.02 to 8.33, P = 0.046). Sepsis was observed in 33.3% with C. difficile and 8.6% without C. difficile, with an adjusted odds ratio (aOR) of 4.64 (95% CI: 1.92 to 11.21, P<0.01). Other outcomes, including UTI, vasopressor support, encephalopathy, seizures, acute respiratory failure, intubation/mechanical ventilation, GI bleeding, Acute Kidney Injury (AKI), Acute Cerebrovascular Accident (CVA), acute liver injury, hepato-/splenomegaly, Acute Myocardial Infarction (MI), and Congestive Heart Failure (CHF), are presented with corresponding aORs and p-values.

Table 3: Risks and Outcomes associated to C. difficile infection in CAR-T therapy

Risks and Outcomes	With C. difficile	Without C. difficile	Unadjusted odds ratio (Univariable analysis)	Adjusted odds ratio (aOR) (Multivariable analysis)
Pneumonia	7/33 (21.2%)	57/652 (8.7%)	2.81 (95 CI: 1.09 to 7.24, P=0.032)	2.91 (95 CI: 1.02 to 8.33, **P=0.046**)
UTI	2/33 (6%)	31/652 (4.8%)	1.29 (95 CI: 0.28 to 5.98, P=0.741)	1.73 (95 CI: 0.39 to 7.69, P=0.469)
Sepsis	11/33 (33.3%)	56/652 (8.6%)	5.32 (95 CI: 2.35 to 12.04, P<0.001)	4.64 (95 CI:1.92 to 11.21, **P<0.01**)
Vasopressor support	1/33 (3%)	21/652 (3.2%)	0.94 (95 CI: 0.13 to 6.73, P= 0.950)	0.81 (95 CI: 0 .13 to 5.25, P=0.826)
Acute respiratory failure	4/33 (12.1%)	54/652 (8.3%)	1.53 (95 CI: 0.55 to 4.25, P= 0.414)	1.19 (95 CI: 0.35 to 4.06, P=0.774)
Intubation/ Mechanical ventilation	4/33 (12.1%)	37/652 (5.7%)	2.29 (95 CI:0 .80 to 6.56, P=0.121)	1.51 (95 CI: 0.43 to 5.30, P=0.515)
AKI (Acute kidney injury)	6/33 (18.1%)	91/652 (14 %)	1.37 (95 CI:0.62 to 3.05, P=0.438)	1.56 (95 CI: 0.67 to 3.66, P=0.301)
GI bleeding	2/33 (6.1%)	12/652 (1.84%)	3.44 (95 CI: 0.82 to 14.58, P=0.093)	2.89 (95 CI:0.70 to 11.97, P=0.142)
Acute liver injury	1/33 (3%)	6/652 (0.9%)	3.36 (95 CI:0.38 to 29.99, P=0.274)	4.27 (95 CI:0.47 to 39.03, P=0.197)
CHF	3/33 (9.1%)	31/652 (4.8%)	2.00 (95 CI: 0.58 to 6.92, P=0.269)	1.71 (95 CI:0.36 to 8.25, P=0.499)
Encephalopathy	11/33 (33.3%)	152/652 (23.3%)	1.64 (95 CI:0.74 to 3.65, P=0.219)	1.58 (95 CI:0 .75 to 3.34, P=0.224)
Seizures	1/33 (3%)	15/652 (2.3%)	1.33 (95 CI:0.17 to 10.60, P=0.788)	1.32 (95 CI:0.13 to 13.35, P= 0.812)
Intracranial hemorrhage	1/33 (3%)	7/652 (1/1%)	2.88 (95 CI:0.32 to 25.60, P= 0.340)	2.34 (95 CI:0.21 to 25.83, P=0.483)

Supplemental Table

Variable	ICD-10 / Procedure codes used
CAR-T therapy	XW033C3, XW043C3
Clostridioides difficile infection	A047, A0471, A0472
Pneumonia	A0103, A0222, A3700, A3701, A3710, A3711, A3780, A3781, A3790, A3791, A5004, A5484, B012, B052, B0681, B7781, J09X1, J100, J110, J12, J13, J14, J15, J16, J17, J18, J8411, J842, J851, J852, J95851, P23
UTI	N39.0, T83.511X, N10, N11.0, N11.1 N12, N28.85, N30
Sepsis	A021, A227, A267, A327, A400, A401, A403, A408, A409, A41,A4101, A4102, A411, A412, A413, A414, A4150, A4151, A4152, A4153, A4159, A4181, A4189, A419, A427, A5486, B377, P360, P3610, P3619, P362, P3630, P3639, P364, P365, P368, P369, R6520, R6521, T8144XA, T8144XD, T8144XS
Vasopressor support	3E030XZ, 3E033XZ, 3E040XZ, 3E043XZ, 3E050XZ, 3E053XZ, 3E060XZ, 3E063XZ
Acute respiratory failure	J9600, J9601, J9602, J9620, J9621, J9622, J9690, J9691, J9692
Intubation/Mechanical ventilation	5A09357, 5A09457, 5A09557, 09HN7BZ, 0CHY7BZ, 0DH57BZ, 0NH17EZ, 5A1935Z, 5A1945Z, 5A1955Z, 0BH07DZ
AKI	N170, N171, N172, N178, N179
Encephalopathy	G92, G93.4, G93.40, G93.41, G93.49
Seizures	G40
Acute liver injury	K7200, K7201, K7290, K7291
CHF	I50, I97. 13
Intracranial hemorrhage	I6000, I6001, I6002, I6010, I6011, I6012, I602, I6030, I6031, I6032, I604, I6050, I6051, I6052, I606, I607, I608, I609, I6030, I6030, I610, I611, I612, I613, I614, I615, I616, I618, I619, I6200, I6201, I6202, I6203, I621, I629
GI bleeding	K920, K921, K922, K625, K928, K929, K9281, K9282, K9289, K250, K254, K260, K264, K270, K28, K621

DISCUSSION

We identified 685 inpatient cases of CAR-T therapy, among which 33 developed C. difficile infection, indicating an incidence of 4.8%. This finding is comparable to other studies, where the incidence of C. diff infection ranged between 12.5%-20%; though it has to be noted that our study encompassed a larger patient population as compared to some of the other studies [2-11]. Interestingly, the occurrence of C.diff in patients treated with CAR-T therapy in our study was lower than the one reported in patients receiving other myelosuppressive therapies for hematological malignancies, which was around 7% [12]. Basic characteristics of the patients were compared. The median age of patients was around 58 years, similar in both groups. This was in alignment with other studies [11]. Among patients with C.diff infections, 21 were males and 10 were females and we observed no significant disparity in incidence rates based on gender when compared to the non C.diff group. No significant difference in incidence of C diff in patients of different races, different median household income, insurance status, geographical location or hospital bed size. There was an increased incidence of C.diff in patients with higher Charlson comorbidity risk, though not significantly different from patients without C diff.

A notable finding in our study revealed a substantial six fold increase in mortality rate in patients with C.diff infection (18.2%) as compared to those without C.diff infections (2.8%). While there is scarcity of studies for direct comparison of mortality rates attributable to C.diff infection, existing evidence suggests a link between severe C.diff infection and infection related death [6]. Additionally, the average length of hospital stay for patients with C.diff infections was higher, approximately 30 days, in contrast to those without C.diff infections, who had an average stay of about 19 days. These findings emphasize the severity of C.diff infections and need for increased awareness and effective management strategies.

We also studied the risks and occurrences of other conditions in the groups with and without C. diff infections. There was an increased incidence of pneumonia (21.2% as compared to 8.7%, with adjusted odds ratio of 2.91 and p value of 0.046) and sepsis (33.3% as compared to 8.6%, with adjusted odds ratio of 4.64 and p value of 0.001). This finding is in alignment with other studies that have found pneumonia to be one of the most common infection sites in CAR-T therapy patients [13]. There was also increased incidence of UTI, complications like acute respiratory failure, intubation/mechanical ventilation, acute kidney injury, GI bleeding, liver injury, congestive heart failure, encephalopathy, intracranial hemorrhage in patients with C.diff infections but did not show any statistically significant difference from patients without C.diff infections.

Based on our study results, it is implied that there is significant risk of C.diff infections in the group receiving CAR-T therapy. Major risk factors that contribute to infections include degree of neutropenia, severity of cytokine release syndrome (CRS), history of administration of corticosteroids and tocilizumab [6-14]. Many institutes administer antimicrobial prophylaxis to neutropenic patients [14], and more data is needed to determine if that can be an independent risk factor for c.diff infections. Limited recommendations exist for treating C.diff infections in cancer patients. According to one of the articles, it is suggested that oral vancomycin may be the preferred first line therapy due to better tolerance and fewer gastrointestinal side effects compared with metronidazole [15]. In a study, oral vancomycin was successfully used for prophylaxis in a patient with a history of recurrent C.diff infections [14].

Our study has unique strengths. We have pioneered investigation of C.diff infections in CAR-T therapy patients, an area that has not been extensively studied before. Our substantial cohort size, thorough comparative analysis and clinically relevant insights may lay a solid foundation for establishing standard guidelines for prevention and management of C. diff infections in these patients.

Limitations

While the National Inpatient Sample (NIS) database provides valuable insights into inpatient hospitalizations, it is not without its limitations. Notably, it lacks information regarding pre-admission and post-discharge details, which restricts our ability to conduct comprehensive long-term follow-up studies. The cross-sectional nature of our data means that our findings establish associations rather than causal relationships with the events under study. The NIS database has limitations related to coding, missing data, and dependency on inpatient admissions, among other factors. In NIS database studies, hospitalizations are the focus rather than individual patients, leading to separate counts for patients admitted multiple times. Additionally, our analyses are based on retrospective registry data, introducing the potential for selection bias due to selective reporting and reliance on ICD codes for defining patient cohorts. Our dataset lacks crucial specifics, such as imaging results, laboratory values, treatment strategies, and cause-of-death analyses. These elements are essential when interpreting our

results and evaluating their implications for clinical practice.

Despite these limitations, our study provides valuable insights into C. difficile infections in patients undergoing CAR T therapy. Our overarching objective is to enhance patient outcomes by offering guidance for clinical decision-making. While acknowledging the presence of coding errors and variations, it is crucial to emphasize that the NIS database remains widely accepted and validated. Our study, based on a substantial sample drawn from this database, represents a diverse population across the United States and incorporates data from numerous medical centers.

CONCLUSION

In summary, our retrospective analysis of CAR-T therapy hospitalizations highlighted the significant impact of C. difficile infections, revealing elevated mortality rates and prolonged hospital stays. While certain complications showed increased risks in the C. difficile group, additional prospective studies are imperative to further understand these associations. The findings from our study emphasize the pressing need for targeted prevention and management strategies for C. difficile infections in patients receiving CAR-T therapy. This investigation contributes to a foundational understanding, emphasizing the importance of future studies to inform comprehensive guidelines for the optimal care of CAR-T therapy patients.

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