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Early administration of the first antimicrobials should be considered a marker of optimal care of patients with community-acquired pneumonia rather than a predictor of outcomes

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SUMMARY

Background: The effect of time of the first antimicrobial dose (TFAD) on the outcomes of community-acquired pneumonia (CAP) remains a controversy.
Methods: This was an observational, retrospective study of consecutive adult patients hospitalized with CAP. TFAD was defined as the time in hours from arrival at the emergency department to the intravenous infusion of antimicrobial. All patients received appropriate antibiotic therapy according to available Infectious Diseases Society of America/American Thoracic Society guidelines during the time of our study. Multivariable analysis and a propensity score adjusted methodology were used to measure the association of TFAD with mortality, time to clinical stability (TCS), and length of stay in the hospital (LOS).
Results: Data of 372 patients with CAP were studied. A total 29 (8.4%) patients died within 30 days of hospitalization. Our propensity-adjusted logistic regression model did not show a significant association between TFAD and mortality ($p = 0.148$). Patients who died received antimicrobials significantly earlier than survivors: 5.7 h vs. 7.5 h, respectively ($p = 0.04$). The LOS and TCS were not significantly affected by the TFAD; the LOS hazard ratio was 0.996 (95% confidence interval 0.97–1.02; $p = 0.774$) and the TCS hazard ratio was 1.01 (95% confidence interval 0.98–1.03; $p = 0.604$).
Conclusions: TFAD does not seem to be associated with the clinical outcome of patients with CAP. Early TFAD should be considered as an important marker of optimal care of patients with CAP rather than as a factor predicting outcomes.

1. Introduction

Community-acquired pneumonia (CAP) is the leading cause of death from infectious diseases in most developed countries.[1–3] Due to the burden of CAP on morbidity and mortality, healthcare providers must adopt practices focused on improving outcomes. A key measure to achieve this target is to optimize the practice of antimicrobial usage. During the past decades, increasing evidence has strengthened the recommendations of guidelines concerning risk factor analysis and appropriate antimicrobial practices.[2,3] There is a logical assumption that early antimicrobial treatment leads to favorable outcomes in CAP, while delayed antimicrobial therapy leads to poor outcomes. The early administration of antimicrobial therapy is expected to be effective in those with an early diagnosis of bacterial pneumonia and in cases with an effective host response. This assumption has not been consistently validated and it has been reported that practices targeting early antimicrobial administration increase the risk of treating cases of suspected pneumonia that are subsequently confirmed not to be.[4,5]

The effect of time of the first antimicrobial dose (TFAD) on the outcome of CAP remains controversial. Two retrospective studies of Medicare beneficiaries demonstrated significantly lower mortality among patients who received early antibiotic therapy.[6,7]

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However, other studies reported different results.[8–11] To further evaluate the correlation of the TFAD with clinical outcomes of patients with CAP, our study examined a cohort of patients with CAP hospitalized at the Louisville Veterans Affairs Medical Center and measured the associations of TFAD with hospital mortality, TCS, and LOS adjusted by propensity models.

2. Materials and methods

This was an observational, retrospective study of consecutive adult patients hospitalized with CAP at the Veterans Affairs Medical Center of Louisville, Kentucky, USA, from June 2001 through March 2006. These patients were enrolled in the Community-Acquired Pneumonia Organization (CAPO) cohort study. The study was approved by the Veterans Affairs Medical Center Institutional Review Board. Data on patient demographic characteristics, risk factors for coronary artery disease, medical co-morbidities, clinical and laboratory variables, radiographic findings, electrocardiogram findings, severity of disease determined on the basis of the pneumonia severity index (PSI) score and the CRB-65 score, microbiological data, time to clinical stability (TCS), duration of hospital stay, clinical failure, mortality at hospital discharge, mortality at 30 days, and acute myocardial infarction (AMI) on hospital admission or during hospital stay were extracted for this study. Copies of the study protocol and data collection form are available at the study web site (http://www.caposite.com).[12]

2.1. Study definitions

CAP was defined as the presence of a new pulmonary infiltrate on chest radiograph at the time of hospital admission and either a new or increased cough with or without sputum production, an abnormal temperature ($<35.6\,^{\circ}C$ or $>37.8\,^{\circ}C$), or an abnormal serum leukocyte count (e.g., leukocytosis, left shift, or leukopenia). The severity of CAP at the time of hospitalization was measured using the PSI score. Severe CAP at the time of hospital admission was defined as the need for admission into the intensive care unit (ICU). Clinical stability was defined as an absence of fever, improved signs and symptoms associated with CAP, and improved leukocyte count. The time of emergency department (ED) arrival was the time recorded in the patient ED registration. The time of the first antibiotic dose was determined from the nurse's notes on timing of the antibiotic administration. TFAD was defined as a continuous variable, indicating the time in hours from arrival to the ED to intravenous (IV) infusion of antimicrobial. TFAD were grouped as: <2 h, >2 h to <4 h, >4 h to <8 h, and >8 h. Patients who received oral or IV antimicrobial therapy before arrival at the ED, or 24 h after arriving at the ED, were excluded.

All patients received appropriate antibiotic therapy according to available Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines during the time of our study.

2.2. Statistical analysis

Baseline characteristics of patients who died versus those who survived were compared using the Chi-square or Fisher's exact tests for categorical variables and the Mann–Whitney *U*-test for continuous variables. To examine the adjusted effect of antimicrobial timing on the outcomes of mortality, TCS, and length of stay in the hospital (LOS), a propensity score adjustment methodology was used. After creation of the propensity score, a logistic regression model was used to examine the propensity-adjusted effect of antimicrobial timing on mortality, while Cox proportional hazards regression models were used for TCS and LOS. *p*-Values of ≤ 0.05 were considered statistically significant. SAS v9.2 (SAS Inc., Cary, NC, USA) was used for all analyses.

Variables included in the propensity score are of known importance in the medical literature and deemed clinically relevant potential confounding variables. Propensity score adjustment was used to control the effects of confounding factors on TFAD and outcomes of CAP.[13] This analysis controlled for the following variables using a propensity-adjusted logistic regression model: age, platelet count, albumin, creatinine, diabetes mellitus, arterial hypertension, corticosteroids, blood urea nitrogen (BUN), AMI, gender, ICU admission, respiratory rate, blood pressure (systolic (SBP) and diastolic), sodium, oxygen saturation, heart rate, nursing home residence, presence of existing diagnoses like cancer, liver disease, congestive heart failure (CHF), cerebrovascular accidents (CVA), renal disease, AMS, chronic obstructive pulmonary disease (COPD), and HIV infection, and indicators of complex pneumonia like multilobar infiltrates, pleural effusion, and cavitary lesions.

3. Results

A total 372 patients with CAP were enrolled during the study period. The main characteristics of the study population are summarized in Table 1. A total 29 (8.4%) patients died within 30 days after hospitalization. The main characteristics of patients are summarized in Table 1. The patients who died tended to be older than survivors: mean age 78 years vs. 68.9 years, respectively. A total of 67 (18.0%) patients were admitted to the ICU.

The mortality of patients admitted to the ICU was 10.4%. ICU admissions were not significantly different between those who died and those who survived. AMS was reported in 33 (8.9%) patients and four of them (12.1%) died. AMS was not significantly different among those who died and those who survived. Neoplastic disease, CHF, AMI, SBP less than 90 mmHg, presence of pleural effusion, arterial blood pH <7.35, BUN >30 mg/dl, and PSI classes IV and V were significantly greater among those who died. PSI classes IV and V were reported in 25 (86.2%) patients who died. However, a CRB-65 score of 2–4 was present in only six (20.7%) patients who died. There were statistically significant differences in PSI class IV and V scores between the two groups, though this was not the case for a CRB-65 score of 2–4.

Our propensity-adjusted logistic regression model did not show any significant association between TFAD with the risk of mortality ($p = 0.148$) (Fig. 1). Similarly the propensity-adjusted logistic regression model corrected by eliminating nursing patients and patients who died within 48 h of hospitalization revealed no significant association between TFAD and the risk of mortality $p = 0.113$ (Fig. 2); nor for patients admitted to ICU p=0.348 (Fig. 3). Patients who died received antimicrobials significant earlier than survivors: 5.7 h versus 7.5 h, respectively ($p = 0.04$). Among survivors, the mean TCS was 3.6 days (SD 2.5) for antimicrobials given in less than 4 h, mean: 3.1 days (SD 2.3) for antimicrobials given between 4 and 8 h, and mean: 2.9 days (SD 2.2) for antimicrobials given after 8 h. In the same group, the mean LOS was 5.9 days (SD 3.9) for antimicrobials at <4 h, mean: 5.1 days (SD 3.5) for antimicrobials given between 4 and 8 h, and mean: 5.6 days (SD: 4.1) for antimicrobials given after 8 h. The LOS and TCS were not significantly affected by the TFAD. The LOS hazard ratio was 0.996 (95% confidence interval 0.97–1.02; $p = 0.774$) and the TCS hazard ratio was 1.01 (95% confidence interval 0.98–1.03; $p = 0.604$).

4. Discussion

Our study measured the correlation of TFAD with mortality, TCS, and LOS of patients with CAP using a propensity-adjusted model controlling for 36 variables. Our cohort study results did not show any correlation of TFAD with the mortality, TCS, or LOS of

Table 1
Characteristics of patients with CAP who died and survived in relation to the time of first antimicrobial dose

Patient characteristics	Variable	Died $n=29$	Survived $n=343$	p-Value
Demographic information				
	Age, years, mean (SD)	78.0 (8.4)	68.9 (12.4)	<0.001
	Male gender	26 (89.7)	338 (98.5)	0.002
Co-morbidities				
	Neoplastic disease	7 (24.1)	35 (10.2)	0.023
	Congestive heart failure	12 (41.4)	82 (23.9)	0.038
	Renal disease	8 (27.6)	51 (14.9)	0.072
	Liver disease	1 (3.4)	9 (2.6)	0.792
	Acute myocardial infarction	5 (17.2)	20 (5.8)	0.018
	Cerebrovascular accident	3 (10.3)	40 (11.7)	0.831
	Chronic obstructive pulmonary disease	14 (48.3)	160 (46.6)	0.866
	Diabetes mellitus	10 (34.5)	122 (35.6)	0.907
	Arterial hypertension	24 (82.8)	236 (68.8)	0.116
	HIV infection	0 (0)	2 (0.6)	0.680
	Nursing home resident	1 (3.4)	14 (4.1)	0.868
Physical findings				
	Altered mental status	4 (13.8)	29 (8.5)	0.332
	Systolic blood pressure <90 mmHg	6 (20.7)	20 (5.8)	0.003
	Heart rate >125 beats/min	2 (6.9)	35 (10.2)	0.568
	Respiratory rate >30 breaths/min	5 (17.2)	32 (9.3)	0.172
	Temperature <35 °C or ≥40 °C	1 (3.5)	6 (1.8)	0.518
Severity of disease				
	Cavitary lesion	1 (3.4)	2 (0.6)	0.098
	Pleural effusion	9 (31)	52 (15.2)	0.027
	ICU admission	7 (24.1)	60 (17.5)	0.371
	Multilobar infiltrates	11 (37.9)	91 (26.5)	0.186
	PSI class IV and V	25 (86.2)	182 (53.1)	<0.001
	CRB-65 score 2–4	6 (20.7)	54 (15.7)	0.440
Laboratory findings				
	PaO_2 <60 mmHg	14 (48.3)	115 (33.5)	0.109
	pH <7.35	3 (10.3)	10 (2.9)	0.036
	BUN ≥30 mg/dl	13 (44.8)	69 (20.1)	0.002
	Sodium <130 mmol/l	0 (0)	23 (6.7)	0.150
	Platelet count, × 10^9/l, mean (SD)	299.5 (175.7)	275.0 (123.5)	0.467
	Albumin, g/dl, mean (SD)	3.27 (0.6)	3.48 (0.6)	0.088
	Creatinine, mg/dl, mean (SD)	1.72 (1.3)	1.53 (1.8)	0.469
Antimicrobial administration				
	≤2 h	3 (10.3)	23 (6.7)	0.254
	>2–4 h	9 (31.0)	62 (18.1)	
	>4–8 h	9 (31.0)	120 (35.0)	
	> 8 h	8 (27.6)	138 (40.2)	
Antimicrobial administration in hours (time mean)	5.7 (3.1)	7.5 (4.3)	0.040	

BUN, blood urea nitrogen; CAP, community-acquired pneumonia; ICU, intensive care unit; PSI, pneumonia severity index; SD, standard deviation.

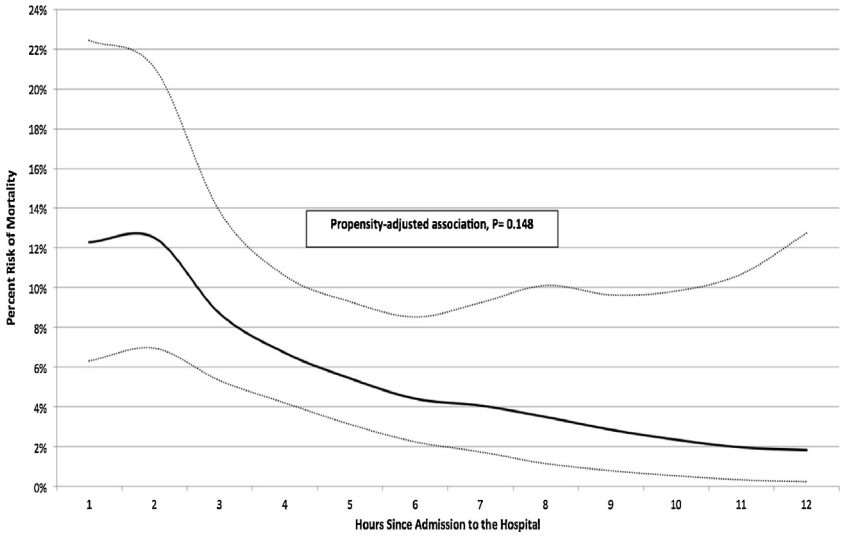


Fig. 1. Propensity-adjusted risk of mortality due to community-acquired pneumonia (CAP) with 95% confidence intervals, by time of first antibiotic dosage (TFAD) upon arrival in the emergency department, for patients hospitalized with CAP at the Veterans Hospital of Louisville, Kentucky, June 2001–March 2006.

patients with CAP. Early or delayed TFAD was not associated with favorable or poor outcomes, respectively.

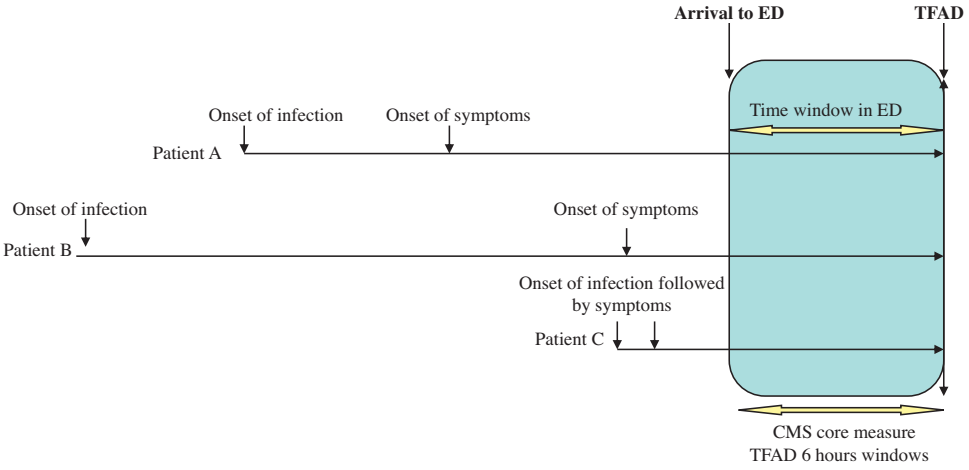
Antimicrobial administration within the first 24 h of diagnosis of CAP was not associated with any changes in the mortality rate, as seen in Fig. 1. The outcomes of CAP may be the result of an equation of multiple factors, and TFAD as a single factor of the equation may not have enough weight to have an effect on the outcomes of CAP. Due to ethical and logistic issues, studies cannot measure the direct effect of TFAD on clinical outcomes of CAP. Interestingly, our study patients who died received antimicrobials significantly earlier than survivors, suggesting that antimicrobials as a single factor do not result in favorable outcomes. It is possible that this counter-intuitive mortality result is due to unmeasured factors not accounted for by the propensity model.

Waterer et al. reported the association of TFAD longer than 4 h with an increasing mortality in a univariate analysis.[14] This association was not significant in the multivariate analysis after controlling for the presence of altered mental status, absence of fever, absence of hypoxia, and increasing age.[14] The latter four factors were examined in our multivariate analysis producing similar results to Waterer et al. and Silber et al.[10,14] Conversely, Houck et al. did not adjust for altered mental status and fever.[6] Though, the strength of the study by Houck et al. is the large sample size, the lack of adjustment for some major confounders may have contributed to the results of decreased 30-day mortality in patients with CAP who received antimicrobials within 4 h.[6] Similar to our results, a prospective study by Bruns et al. demonstrated that TFAD within the first 4 h does not predict early clinical stability, lower risk of ICU admission, or lower mortality on day 3 in patients with moderate to severe CAP.[8] Our results of outcomes of CAP in relation to TFAD are similar to those reported by others.[10,11]

Although our results demonstrated a lack of correlation between TFAD and the clinical outcomes of CAP, we do not recommend that antimicrobial treatment be delayed. Early antimicrobial administration to patients with CAP is in fact a good marker of quality of medical care.

Regardless of our study results, we consider that starting early antimicrobial treatment is expected to contribute to an improvement in the outcome of CAP. However, early TFAD from the time of ED arrival as a single factor may be a misleading oversimplification since the infection and illness process begin at a variable time before arrival in the ED (Fig. 2). The timing in CAP is a multistep process that goes from establishment of infection, to onset of symptoms and arrival in the ED, to TFAD. Therefore TFAD after arrival in the ED is not a reliable objective measure of this multistep process to control the outcomes of patients with CAP. We suggest TFAD should be considered as an important marker of optimal care of patients with CAP rather than as an intervention factor to control the outcomes. Centers for Medicare and Medicaid Service (CMS) core measures for CAP include the administration of the initial antimicrobial within the first 6 h of ED arrival.[6,7,15] This measure resulted in over-diagnosis of pneumonia in cases with respiratory symptoms and the overuse of antimicrobials by ED physicians to comply with CMS core measures for reimbursement.[16] The priority of the management of patients with presumptive pneumonia should be to increase the accuracy of the diagnosis of CAP for appropriate and timely antimicrobial therapy. We agree with the 2007 IDSA guidelines for CAP that TFAD should be given while the patient is in the ED.[3] Fluid management, adequacy of nutrition, functional status, immune status, and co-morbid conditions, among others, should be considered in addition to TFAD as factors resulting in the outcomes of CAP. Ours as well as other studies have shown independent relationships between outcomes of CAP and several co-morbid conditions like CHF, neoplastic diseases, and elevated BUN at presentation.[17–19]

Limitations of our study include the use of an observational database and a small sample size of patients who died. Strengths of our study include the use of a propensity score to adjust for confounders of a small sample size of patients who died. In addition, our study spanned all severities of disease in adults, including those admitted to the ICU. Another limitation of our study is not including the Food and Drug Administration (FDA) criteria for the diagnosis of CAP. Some of our patients may not have



The time frames vary for patients having different onset of the infection and different onset of symptoms. e.g.

1. Patient A had onset of pneumonia and symptoms much before arrival to ED

2. Patient B had onset of pneumonia long before arrival to ED but symptoms just manifested before arrival to ED

3. Patient C had onset of pneumonia and symptoms just before arrival to ED

A 6 hours TFAD of patients arriving to ED is not expected to be the single factor resulting in the outcomes of CAP.

TFAD: Time of first antibiotic dose. ED: Emergency Department.

Fig. 2. This figure illustrates that despite patients receiving a first antibiotic dosage at the same time upon arrival in the emergency department, the process of pneumonia and onset of symptoms may vary and hence the time of first antibiotic dosage is not the optimal measurement and factor to predict the outcomes of pneumonia.

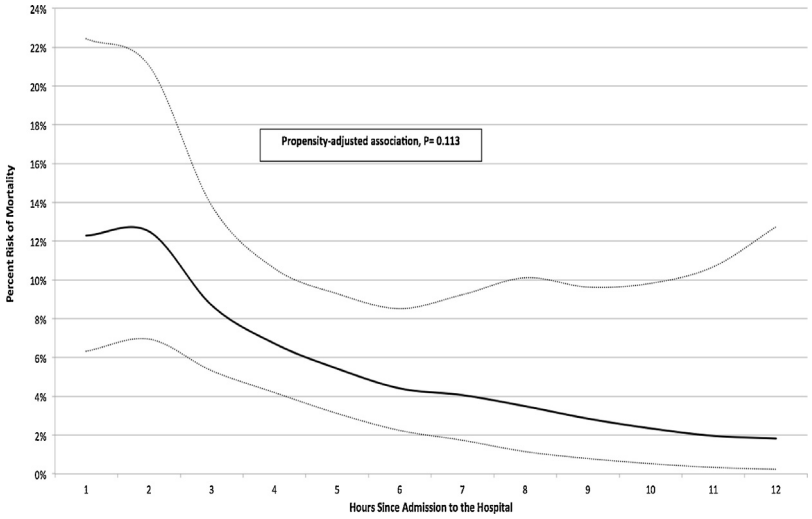


Fig. 3. Propensity-adjusted risk of mortality due to community-acquired pneumonia (CAP) with 95% confidence intervals by time of first antibiotic dosage (TFAD) upon arrival in the emergency department for patients hospitalized with CAP at the Veterans Hospital of Louisville, Kentucky, June 2001–March 2006 after eliminating patients from nursing homes and death within 48 h of hospitalization.

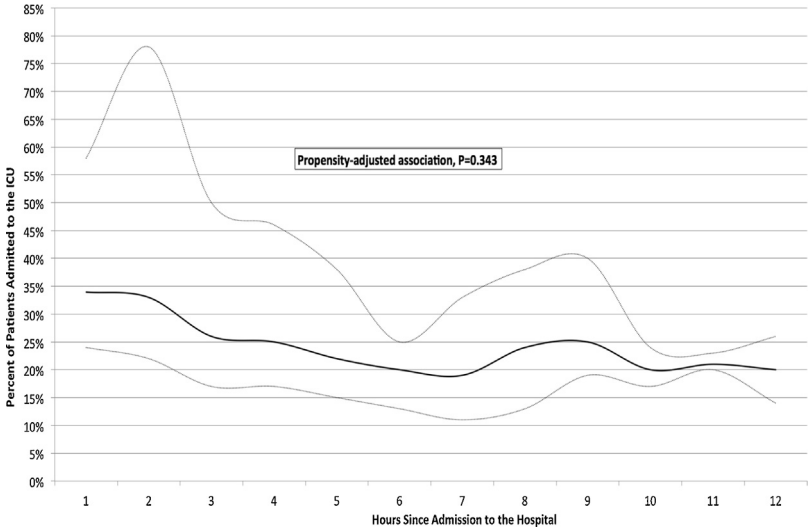


Fig. 4. Propensity-adjusted risk of admission to the intensive care unit with 95% confidence intervals by time of first antibiotic dosage (TFAD) upon arrival in the emergency department for patients hospitalized with community-acquired pneumonia (CAP) at the Veterans Hospital of Louisville, Kentucky, June 2001–March 2006.

fulfilled the stringent criteria for the diagnosis of CAP using the FDA criteria and there is a possibility that clinical improvement in some of our patients was not due to antimicrobial therapy. Our database does not hold data on code status or advance directives; these are currently being implemented in our database. Our study did not adjust for the effect of patient 'do not resuscitate' (DNR) on the outcomes of CAP. We recognize that the presence of a DNR upon arrival in the ED may have had an impact on the outcome of CAP (Figs. 3 and 4).

In conclusion, our study did not show any association between TFAD and the clinical outcomes of patients with CAP. Early TFAD as a single factor does not seem to be an intervention factor to control the outcomes of patients with CAP. Early TFAD should be considered as an important marker of optimal patient care in patients with CAP rather than a factor predicting the outcome.

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Ethical approval: The study was approved by the Veterans Administration Medical Center Institutional Review Board. There were no animals used in the study so ethical consent and standards of animal care do not apply.

Conflict of interest: None of the participating authors have any conflict of interest.

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