Long-Term Cognitive Impairment after Hospitalization for Community-Acquired Pneumonia: a Prospective Cohort Study

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BACKGROUND: Recent studies suggest older patients hospitalized for community-acquired pneumonia are at risk for new-onset cognitive impairment. The characteristics of long-term cognitive impairment after pneumonia, however, have not been elucidated.

OBJECTIVE: To characterize long-term cognitive impairment among adults of all ages hospitalized for community-acquired pneumonia.

DESIGN: Prospective cohort study.

PARTICIPANTS: Adults without severe preexisting cognitive impairment who were hospitalized with community-acquired pneumonia.

MAIN MEASURES: At enrollment, we estimated baseline cognitive function with the Short Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). At 2- and 12-month follow-up, we assessed cognition using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and tests of executive function, diagnosing cognitive impairment when results were ≥ 1.5 standard deviations below published age-adjusted means for the general population. We also identified subtypes of mild cognitive impairment using standard definitions.

KEY RESULTS: We assessed 58 (73%) of 80 patients who survived to 2-month follow-up and 57 (77%) of 74 who survived to 12-month follow-up. The median [range] age of survivors tested was 57 [19–97] years. Only 8 (12%) had evidence of mild cognitive impairment at baseline according to the Short IQCODE, but 21 (38%) at 2 months and 17 (30%) at 12 months had mild cognitive impairment per the RBANS. Moderate-to-severe cognitive impairment was common among adults ≥ 65 years [4/13 (31%) and

5/13 (38%) at 2 and 12 months, respectively] but also affected many of those < 65 years [10/43 (23%) and 8/43 (19%) at 2 and 12 months, respectively]. Deficits were most often noted in visuospatial function, attention, and memory.

CONCLUSIONS: A year after hospitalization for community-acquired pneumonia, moderate-to-severe impairment in multiple cognitive domains affected one-third of patients ≥ 65 years old and 20% of younger patients, and another third of survivors had mild cognitive impairment.

KEY WORDS: pneumonia; cognition disorders; mild cognitive impairment; dementia; hospitalization.
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Community-acquired pneumonia (CAP) is a major source of morbidity and mortality. Each year, over a million hospitalizations in the US alone are attributable to this common infectious disease.^{1–3} Most studies of CAP outcomes have limited follow-up to in-hospital or 30-day outcomes,⁴ and the body of literature that has examined long-term outcomes after CAP has focused primarily on mortality.^{5–7} Yet, many patients who survive hospitalization for CAP struggle with diminished cognitive and functional abilities for prolonged periods after their acute illness.^{8–10}

Numerous reports have shown that survivors of acute respiratory failure and sepsis, which are often caused by pneumonia, are at high risk for cognitive impairment that lasts years after discharge from the ICU and hospital.^{11–16} In addition, several recent studies found that older adults hospitalized for CAP, many of whom were admitted to general medical floors

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without overt organ failure, also experienced persistent declines in cognition.^{8–10} These reports, however, were limited by their use of brief screening tests of cognition, which (unlike comprehensive cognitive batteries) are unable to identify the specific domains of cognition that are impaired in survivors of CAP. Additionally, these earlier studies focused specifically on older patients. Thus, it remains unknown whether younger adults who are hospitalized with CAP are also at risk for subsequent cognitive impairment.

We conducted the Cognitive Outcomes after Community-Acquired Pneumonia (CogCAP) Study to determine the prevalence and severity of long-term cognitive impairment in adults up to 1 year after hospitalization for CAP. We hypothesized that long-term cognitive impairment in this population—the majority of which does not require intensive care—is common and affects multiple cognitive domains.

METHODS

Study Design and Population

We nested this single-center study within a larger prospective cohort study, the Centers for Disease Control and Prevention (CDC) Etiology of Pneumonia in the Community (EPIC) Study.¹⁷ The EPIC study was a multicenter investigation designed to determine the incidence and etiologies of CAP resulting in hospitalization in the US. From January 2010 to June 2012, patients admitted to the Vanderbilt University Medical Center were enrolled in the EPIC Study if they lived in the surrounding nine-county catchment area and had community-acquired pneumonia, defined as evidence of acute infection with signs/symptoms of acute respiratory illness and radiologic evidence of pneumonia, confirmed by a board-certified chest radiologist who was unaware of the clinical data. Exclusion criteria included recent hospitalization; immunosuppression due to malignancy, recent organ or stem cell transplant, or human immunodeficiency virus infection with a CD4 cell count < 200/mm³; nursing home residence with functional dependence; or lack of informed consent, as previously described.¹⁷

Beginning in March 2011, adults enrolled in EPIC at Vanderbilt University were eligible for inclusion in the CogCAP Study if they survived to hospital discharge and had none of the following exclusion criteria: severe cognitive or neurodegenerative disease that prevented independent living prior to CAP (according to medical records and/or an authorized representative); active substance abuse, psychotic disorder, homelessness, or plans to move out of the catchment area within 12 months of enrollment, any of which could prevent long-term follow-up; blindness or deafness, which would prevent outcomes assessment; lack of commitment to aggressive treatment (e.g., discharge to hospice); or lack of informed consent.

Patients were enrolled in the EPIC study within 24 h of hospital admission, but we did not enroll patients in CogCAP

until 1 to 2 days prior to discharge, at which time we obtained separate written informed consent for CogCAP participation. The Vanderbilt University and CDC Institutional Review Boards approved the study protocol.

Baseline and In-Hospital Assessments

At enrollment, a trained psychology professional evaluated participants' baseline (i.e., pre-CAP hospitalization) cognitive and functional status using the following questionnaires, validated to assess pre-illness status. We assessed baseline global cognition with the Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE),¹⁸ baseline activities of daily living (ADLs) with the Katz ADL questionnaire,¹⁹ and baseline instrumental ADLs with the Functional Activities Questionnaire (FAQ).²⁰ Both participants (when able) and surrogates (e.g., a family member or close friend) completed questionnaires; if a questionnaire's score differed between the participant and surrogate, we used the worst score to maximize sensitivity.

We obtained demographic and clinical data from the medical record. These included data required to calculate the Charlson Comorbidity Index,²¹ which summarizes the total burden of comorbid illness prior to hospitalization by assigning points to specific chronic conditions (e.g., 1 point for congestive heart failure, 3 points for moderate-to-severe liver disease, and 6 points for metastatic solid malignancy), and the Pneumonia Severity Index,⁴ a severity of illness measure that has been validated in several community-acquired pneumonia cohorts.

Outcomes

Two and 12 months after hospital discharge, psychology professionals assessed participants' cognition using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS),²² a comprehensive, validated battery that evaluates five domains of cognitive function: immediate memory, delayed memory, attention, visuospatial construction, and language (described in detail in eTable 1). In addition, we also used the Mini-Mental State Examination (MMSE) to assess general cognition, the Trail Making Test A²³ to assess attention, the Trail Making Test B²³ and the Tower Test (a subtest of the Delis-Kaplan Executive Function System²⁴) to assess executive function, the Katz Activities of Daily Living¹⁹ and the Functional Activities Questionnaire²⁰ to assess activities of daily living and instrumental activities of daily living, and the Short IQCODE¹⁸ to assess self-reported changes in cognition.

Statistical Analysis

To determine whether patients who were tested during follow-up were different from those who were not, we used Fisher's exact tests to compare categorical variables and Wilcoxon rank-sum tests to compare continuous variables.

We categorized patients as having mild cognitive impairment at baseline if either their patient-based or surrogate-based Short IQCODE was > 3.6 ; overall scores were obtained by averaging the scores of individual items. Following conventional neuropsychologic research methods, we compared participants' results for each test to published age-adjusted norms for the general population and considered results ≥ 1.5 standard deviations below age-adjusted population means to indicate impairment. Per published norms, 6.7% of the general population is expected to score below this cutoff. We identified mild cognitive impairment (which we subdivided into four mutually exclusive subtypes) using the standard definitions described in eTable 2,²⁵ and we defined "moderate-to-severe" cognitive impairment as that resulting in RBANS global index scores < 78 .

We used Stata Statistical Software (Release 10.1; StataCorp LP, College Station, TX) for all statistical analyses.

RESULTS

Between March 2011 and June 2012, 265 adults admitted to Vanderbilt University Medical Center with CAP were enrolled in the EPIC study. Of these, we enrolled 86 (32%) in the CogCAP Study; 72 were not approached because of lack of staffing (e.g., they were discharged when CogCAP study personnel were not available), 63 declined to participate in the long-term study, and 44 were excluded for reasons shown in Fig. 1. Six (7%) of the 86 patients enrolled in CogCAP died within 2 months of hospital discharge, and 7 (8%) others died

between 2 and 12 months, such that 80 subjects were eligible for follow-up at 2 months and 73 were eligible at 12 months. Of these, we assessed 58 (73%) 2-month survivors and 57 (78%) 12-month survivors. Participants who were alive but not assessed at 2 and/or 12 months were unable or unwilling to participate in the follow-up visit or were no longer reachable by study personnel.

The follow-up cohort included 67 subjects tested at 2 months and/or 12 months (Table 1). Patients with a broad range of ages were included, the median [interquartile] age being 57 [48–64] years and the range spanning from 19 to 97 years of age. Eighteen (27%) subjects had no comorbid illness at baseline (Charlson Comorbidity Index = 0), another 27% had only one comorbidity (Charlson Index = 1), and 46% had multiple comorbidities (Charlson Index ≥ 2). Though patients with moderate/severe preexisting cognitive impairment (e.g., neurodegenerative disease that prevented independent living) were excluded, those with mild cognitive impairment at time of CAP hospitalization were eligible, with eight (12%) patients having a Short IQCODE > 3.6 suggesting some cognitive impairment at baseline.

Compared with those assessed at follow-up, patients who were never tested because of post-discharge death were more severely ill at admission per their Pneumonia Severity Index, ICU admission status, and need for invasive mechanical ventilation (eTable 3). Alternatively, patients who survived but were never tested (i.e., lost to follow-up) were not significantly different from those tested (eTable 4).

At 2-month follow-up, 14 (24%) of 56 patients assessed had RBANS global cognition scores indicating moderate-to-severe cognitive impairment (Tables 2 and 3). In contrast, published norms indicate that $< 7\%$ of the general population has RBANS global cognition scores in this range. At 12 months, 13 (23%) of 56 had scores consistent with moderate-to-severe cognitive impairment. At 2-month

Figure 1 Enrollment and follow-up

Table 1 Characteristics of Patients Assessed 2 to 12 Months after Hospitalization with Community-Acquired Pneumonia

Characteristic	No. = 67
Age, median [IQR], years	57 [48–64]
Female, no. (%)	40 (60)
Race, no. (%)	
White	41 (61)
Black	24 (36)
Other	2 (3)
Charlson Comorbidity Index, median [IQR]	1 [0–3]
Baseline cognitive impairment, no. (%)	8 (12)
Pneumonia Severity Index, no. (%)	
Low risk (1–2)	31 (46)
Moderate risk (3)	19 (28)
High risk (4–5)	17 (25)
Presenting systolic blood pressure < 90 mmHg, no. (%)	0
Presenting oxygen saturation $< 90\%$, no. (%)	3 (4)
Presenting white blood cell count $> 11,000$ cells/mcl, no. (%)	43 (64)
Serum procalcitonin > 0.25 ng/ml, no. (%)	36 (54)
ICU admission, no. (%)	14 (21)
Invasive mechanical ventilation, no. (%)	2 (3)
Vasopressor use, no. (%)	3 (4)
Hospital length of stay, median [IQR], days	3 [2–5]

Table 2 Cognitive Scores after Hospitalization for Pneumonia

Outcome ^a	2 months	12 months
RBANS scores ^b		
Global cognition	86 [77, 95]	87 [79, 94]
Impaired, no. (%)	14 (25)	13 (23)
Immediate memory	94 [83, 106]	97 [85, 109]
Impaired, no. (%)	6 (10)	6 (11)
Delayed memory	92 [83, 95]	94 [88, 101]
Impaired, no. (%)	8 (14)	5 (9)
Visuospatial function	69 [64, 81]	75 [66, 78]
Impaired, no. (%)	37 (64)	33 (58)
Attention	97 [82, 109]	94 [85, 103]
Impaired, no. (%)	6 (11)	6 (11)
Language	96 [88, 104]	92 [84, 99]
Impaired, no. (%)	5 (9)	4 (7)
Other cognitive test scores		
Trails A (attention) ^c	45 [37, 50]	47 [38, 53]
Impaired, no. (%)	9 (16)	12 (21)
Trails B (task switching) ^c	48 [40, 54]	49 [43, 55]
Impaired, no. (%)	7 (13)	5 (9)
Tower achievement (planning) ^d	10 [9, 12]	11 [9, 12]
Impaired, no. (%)	2 (4)	3 (5)

Abbreviations: RBANS repeatable battery for the assessment of neuropsychologic status

^aPresented as median [interquartile range] unless otherwise noted

^bRBANS scores are age-adjusted and have a population mean $\pm$ SD of 100 ± 15 , with lower scores indicating worse cognition. Per published norms, 6.7% of the general population is expected to score below the cutoff we used to identify "impaired"

^cTrails A and B scores are age-adjusted and have a population mean $\pm$ SD of 50 ± 10 , with lower scores indicating worse cognition. Per published norms, 6.7% of the general population is expected to score below the cutoff we used to identify "impaired"

^dTower Achievement scores are age-adjusted and have a population mean $\pm$ SD of 10 ± 3 , with lower scores indicating worse cognition. Per published norms, 6.7% of the general population is expected to score below the cutoff we used to identify "impaired"

follow-up, 20 (36%) of 56 patients had deficits in two or more cognitive domains, and 9 (16%) had deficits in three or more domains. Similarly, 16 (29%) of 56 patients assessed at 12 months had deficits in two or more cognitive domains, and 9 (16%) had deficits in three or more domains. Visuospatial function, attention, and memory were the most frequently

Table 3 Long-Term Cognitive Impairment after Hospitalization for Pneumonia

Outcome	2 months	12 months
No impairment, no. (%)	21 (38%)	26 (46%)
Mild cognitive impairment, ^a no. (%)	21 (38%)	17 (30%)
Amnesic, single domain	0 (0%)	0 (0%)
Amnesic, multiple domains	2 (4%)	0 (0%)
Non-amnesic, single domain	15 (27%)	13 (23%)
Non-amnesic, multiple domains	4 (7%)	4 (7%)
Moderate/severe cognitive impairment, ^b no. (%)	14 (25%)	13 (23%)
Without IADL disability ^c	12 (21%)	11 (20%)
With IADL disability ^c	2 (4%)	2 (4%)

Abbreviations: IADL instrumental activities of daily living, MCI mild cognitive impairment

^aWe classified patients as having mild cognitive impairment using standard definitions²⁵ (see eTable 2)

^bWe classified patients as having moderate/severe impairment if their Repeatable Battery for the Assessment of Neuropsychological Status global cognition score was < 78 (an established cutoff)

^cWe identified IADL disability using the Functional Activities Questionnaire

impaired domains, whereas language and executive function/planning were infrequently impaired (Table 2).

Though older patients (≥ 65 years) with multiple comorbidities had the lowest RBANS global cognition scores throughout follow-up, younger patients without comorbid illness also had scores lower (i.e., worse) than expected based on population norms (Fig. 2). At both 2 and 12 months, moderate-to-severe cognitive impairment was most common among adults ≥ 65 years old [4/13 (31%) and 5/13 (38%), respectively] but also affected those < 65 years old [10/43 (23%) and 8/43 (19%), respectively].

Mild cognitive impairment was also common, noted in more than one-third of subjects during each follow-up visit (Table 3). Of the 21 patients with mild cognitive impairment according to 2-month RBANS results, only two had evidence of mild cognitive impairment at baseline based on Short IQCODE responses completed in the hospital after the onset of CAP. Similarly, only 1 of the 21 with mild cognitive impairment at 12-month follow-up had impairment at baseline. Memory impairment was common, but mild cognitive impairment rarely met amnesic subtype criteria because patients with memory deficits typically had moderate-to-severe rather than mild cognitive impairment. Non-amnesic mild

Figure 2 Cognitive function 2 and 12 months after community-acquired pneumonia according to age and comorbid illness burden per the Charlson Comorbidity Index. *The Charlson Comorbidity Index was measured at baseline; range 0–33, 0 = no comorbidities, 1 = one comorbidity. †Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Global Cognition Score; age-adjusted population mean $\pm$ SD is 100 ± 15 , with lower scores indicating worse cognition. The dashed line marked TBI indicates the expected population mean for moderate traumatic brain injury, and the dashed line marked AD indicates the expected population mean for mild Alzheimer's disease based on data collected in other cohort studies. The latter is shown only for patients ≥ 65 years of age since RBANS population norms for AD were generated in that age group.

cognitive impairment in a single domain was primarily due to visuospatial function deficits.

DISCUSSION

In this prospective cohort study, we found that one out of every four adults hospitalized with CAP had moderate-to-severe cognitive impairment that persisted at least a year after CAP and another third had mild cognitive impairment. The deficits in cognition were wide ranging and affected multiple domains. In addition, cognitive impairment was present in both older and younger adults, many of whom had no comorbid conditions prior to CAP, and was not limited to patients who were critically ill. These results highlight the need for future research examining mechanisms that may explain the relationship between pneumonia and long-term cognitive impairment as well as interventions that may prevent or mitigate this adverse long-term outcome.

The long-term cognitive impairment observed in our cohort likely has important effects. Though mild cognitive impairment, by definition, does not limit activities of daily living (e.g., eating, bathing, etc.), symptoms can include noticeable decrements in cognitive abilities used each day in driving, managing finances, and completing multistep tasks, e.g., preparing a meal or planning an event, etc. More severe cognitive impairment can, of course, lead to pronounced functional limitations. In the setting of moderate-to-severe cognitive impairment—identified in 25% of our cohort—financial errors, for example, would go beyond bookkeeping mistakes to involve errors in judgment, and problems cooking would involve not just poor planning but repeatedly forgetting to turn off the stove. Since our study reveals that middle-aged adults are at risk for post-CAP cognitive impairment, future studies should assess the impact of CAP hospitalization on patients' ability to return to work and/or their regular daily activities.

In addition to being consistent with results from earlier reports, our study extends previous observations by being the first to use a comprehensive cognitive battery to examine the frequency and characteristics of cognitive impairment in adults of all ages who survived a CAP hospitalization. Because we examined a population that was younger and less severely ill than those previously studied, our results suggest that the problem of post-acute illness cognitive impairment is more far reaching than previously thought. A number of studies have shown that up to half of patients who survive critical illness requiring mechanical ventilation struggle with significant cognitive impairment months to years after their hospitalization.^{14,16} In addition, Elhenbach et al.²⁶ demonstrated that poor cognitive outcomes are not limited to just ICU patients; in their prospective cohort study of 2929 older adults without dementia at baseline, an acute care hospitalization was associated with a significant decline in cognitive function and was identified as an independent risk factor for incident dementia. CAP, one of the most common causes of

such hospitalizations, may be particularly prone to cause declines in cognition via hypoxia,^{27,28} inflammation,^{29,30} and other mechanisms³¹ of organ dysfunction attributable to pneumonia.

Prior to our investigation, three studies examined whether older patients hospitalized for CAP had changes in cognition, but none of these studies were designed to evaluate characteristics of post-CAP cognitive impairment (e.g., specific cognitive domains, subtypes of mild cognitive impairment, etc.) nor did they examine younger adults with CAP. Davydow and colleagues⁸ analyzed cognitive outcomes measured in the Health and Retirement Study to determine whether patients hospitalized with CAP during this long-term longitudinal study of patients > 50 years of age had declines in cognition associated with CAP. After adjusting for multiple potential confounders, CAP hospitalization was associated with a 2.46-fold increase in the odds of moderate-to-severe cognitive impairment, which affected 25% of patients after CAP. Similarly, Shah and coworkers⁹ analyzed data from the Cardiovascular Health Study, a long-term longitudinal study of patients ≥ 65 years of age and found CAP was associated with a 1.57-fold increase in the hazard of dementia (diagnosed in 12% of CAP survivors) after adjusting for potential confounders. Finally, Tate et al.¹⁰ assessed healthy volunteers 75 years and older enrolled in a dementia trial and found that CAP hospitalization was associated with a 1.9-fold increase in the hazard of dementia. Importantly, each of these studies tested patients' cognition before and after hospitalization for CAP so that cognitive decline related to CAP could be identified.

In our study, we found that long-term cognitive impairment affecting survivors of CAP had a pattern of deficits similar to that seen in post-critical illness cognitive impairment (also known as critical illness brain injury)³²; i.e., deficits were present in multiple domains of cognition. This pattern is more similar to that observed in traumatic brain injury than in indolent forms of cognitive impairment, e.g., Alzheimer's disease, which primarily affects memory until late in the disease. Whereas approximately one in four patients in our study had moderate-to-severe cognitive impairment 1 year after CAP, more than one in three survivors of critical illness had cognitive impairment at 1 year in a recent, large cohort study.¹⁶ Our study was not sufficiently powered to test whether the high severity of illness common to ICU patients is an independent risk factor for post-CAP cognitive impairment. Nevertheless, one potential explanation for our results is that threats to organ function common in severe critical illness—e.g., hypoxemia, inflammation-driven microvascular thrombosis, mitochondrial dysfunction, among others—may also be pathogenic mechanisms underlying cognitive impairment in survivors of pneumonia. Indeed, both hypoxia and inflammation are risk factors for cognitive impairment after sepsis and in other settings.^{27–30}

Strengths of our study include the use of a rigorous definition of CAP to identify the study population,¹⁷ inclusion of both younger and older adults without evidence of preexisting

cognitive impairment, and use of a well-validated instrument to evaluate patients for preexisting cognitive impairment. Additionally, though even more rigorous and in-depth batteries are available, we employed a widely used, comprehensive battery of cognitive tests, which allowed for detailed characterization of cognitive impairment as well as comparison with other populations, e.g., those with traumatic brain injury or Alzheimer's disease. Like most other investigations of acute illnesses,^{11–14,16} we were limited in our ability to directly assess baseline cognition since occurrence of CAP is rarely predictable. As done in prior studies, we therefore excluded patients with preexisting cognitive impairment severe enough to prevent independent living and relied on a validated questionnaire¹⁸ to identify baseline mild cognitive impairment at time of CAP hospitalization. Despite these efforts, we cannot rule out the possibility that some proportion of the mild cognitive impairment observed in one-third of patients during follow-up was present prior to CAP. Indeed, our results suggest that 12% of participants had mild cognitive impairment prior to being hospitalized with CAP. Though delirium has been shown to predict long-term cognitive impairment after acute and critical illness, we were unable to study this relationship during the current investigation because delirium often goes undiagnosed when patients are not assessed systematically using a validated tool, which we did not employ during this study. Additionally, our study was not powered to analyze the relationship between long-term cognitive outcomes and delirium or other potential risk factors, which should be examined in future, larger investigations. Since patients ≥ 65 years old and those mechanically ventilated were less likely to be enrolled in the EPIC study,¹⁷ our findings may underestimate the overall prevalence of cognitive impairment in CAP survivors. Since we enrolled patients at only one urban tertiary care center, it is unclear if these results are generalizable to other settings. Finally, a number of subjects withdrew or were lost to follow-up; though these subjects did not differ from those assessed in any measurable way, our results may have been biased if cognitive impairment was more (or less) likely among those not assessed during follow-up than among those evaluated.

In conclusion, long-term cognitive impairment, which varies in severity from mild to severe, is common in patients who were hospitalized for CAP, with moderate-to-severe impairment affecting one in four survivors 1 year after hospital discharge. Similar to ICU patients with respiratory failure requiring mechanical ventilation, CAP patients are at high risk for impairment in multiple domains of cognition, including memory, attention, and visuospatial function. In addition to examining mechanisms that may explain the relationship between long-term cognitive impairment and CAP, future studies should seek to identify potentially modifiable risk factors for this potentially life-altering outcome.

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Compliance with Ethical Standards:

Prior Presentations: Some of the results of this study were previously reported in the form of an abstract at the American Thoracic Society 2015 International Conference on May 20, 2015.

Conflicts of Interest: The authors declare that they do not have a conflict of interest.

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