

Role of serum proadrenomedullin in assessment of the severity and outcome of hospitalized healthcare-associated pneumonia patients

Amany Shaker^a, Doaa Mostafa Gad^a, Sameh Embarak^a, Hany A. Labib^b

Background Clinical judgment of healthcare-associated pneumonia (*HCAP*) represents a major concern as these fragile patients have an unusual presentation that frequently misleads severity assessment and results in poor clinical outcome. The aim of this study was to evaluate the role of proadrenomedullin (proADM) in predicting disease severity and outcome in *HCAP* patients in comparison with community-acquired pneumonia (CAP) patients.

Patients and methods Thirty-one *HCAP* patients and twenty-five CAP patients were enrolled in this study. Measurement of serum proADM level was performed in the first 24-h of admission. Assessment of severity was carried out using the CURB-65 scoring system. Finally, the outcome of the patients was assessed.

Results Serum proADM level was higher in *HCAP* patients than that in CAP patients, this difference was statistically significant. Also, serum proADM level increased significantly with increasing severity of *HCAP* patients guided by CURB-65, with a cut-off value of more than 1.8 nmol/l, with a sensitivity of 91.7%, a specificity of 95%, a

positive predictive value of 91.7%, and a negative predictive value of 95%. However, a higher value (>2.9 nmol/l) was detected in *HCAP* patients who died, with high sensitivity and negative predictive value (100%) and low specificity (42.3%) and positive predictive value (25%).

Conclusion The use of proADM as a novel biomarker enhances the performance of the CURB-65 scoring system for risk stratification of *HCAP* patients.

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Departments of ^aChest, ^bClinical Pathology, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Correspondence to Sameh Embarak, MD, Department of Chest, Faculty of Medicine, Zagazig University, Zagazig, 44511, Egypt

Tel: +20 111 168 0540; Fax: +2055-2307-830;

e-mail: sembarak75@yahoo.com

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Introduction

Pneumonias have been classified as community-acquired pneumonia (CAP) and hospital-acquired pneumonia, and this classification is used for proper diagnosis and treatment decisions [1]. However, when pneumonia is associated with healthcare risk factors such as previous hospitalization, residing in a nursing home, receiving outpatient parenteral therapy, attending a hemodialysis clinic, or receiving domiciliary care, it becomes more complex [2]. The American Thoracic Society and the Infectious Disease Society of America had proposed healthcare-associated pneumonia (*HCAP*) as a new pneumonia classification for patients from the community who had recent contact with the healthcare system [3].

Clinical judgment of *HCAP* represents a major concern as these fragile patients have an unusual clinical presentation that frequently misleads severity assessment and results in poor clinical outcome [4]. Despite the latest advances in antimicrobial therapy and improved supportive care, *HCAP* is still a major cause of morbidity and mortality twice as higher than those observed in CAP [5]. Therefore, early identification of patients at high risk is a key point in improving their outcome. Several generic severity

scoring systems have been developed to determine patients' outcome, but they may be complicated for use in everyday practice [6]. Moreover, these scores may underestimate severity assessment in young patients and perform less well when considering outcomes such as ICU admission and mechanical ventilation (MV) [7]. Thus, biomarkers are gaining importance in improving the prognostic accuracy of clinical scores [6]. Adrenomedullin (ADM) is a vasoactive hormone that is predominantly released by the endothelium during physiological stress and acts as a potent vasodilator with natriuretic effects [8]; moreover, it reduces endothelial permeability [9], exerts bactericidal effects [10], and downregulates proinflammatory cytokines [11].

Proadrenomedullin (proADM) is considered good for the determination of severity scores in identifying critically ill patients with CAP and is probably better than other biomarkers used such as procalcitonin and C-reactive protein [6]. In addition, it has greater discriminatory power in predicting serious complications in CAP patients than the pneumonia severity index (PSI) and CURB-65 scores [12]. These findings may be used to decide on the management of the patient, especially for patients with low severity scores and high levels of

biomarkers, as the decision to treat these cases as outpatients should be considered [13]. Therefore, this study aimed to evaluate the role of proADM in predicting disease severity and outcome in *HCAP* patients compared with CAP patients.

Patients and methods

Patients

The current study was carried out at the Chest Department (hospital ward and respiratory ICU) and the Clinical Pathology Department, Zagazig University Hospitals, between December 2010 and December 2012. It included 31 *HCAP* patients, 20 men and 11 women, mean age 64.1 ± 9.8 years, and 25 CAP patients (with no history or clinical evidence of comorbidities), 15 men and 10 women, mean age 57.4 ± 10.9 years.

Patients were recruited according to the diagnostic criteria of CAP and *HCAP*.

CAP was defined by the presence of at least one respiratory symptom (cough, sputum production, dyspnea, tachypnea, pleuritic pain) plus at least one finding during auscultation (rales, crepitation), or one sign of infection (core body temperature $>38.0^{\circ}\text{C}$, shivering, leukocyte count >10 or $<4 \times 10^9$ cells/l) along with a new infiltrate on the chest radiograph [14].

HCAP was defined as patients admitted to the hospital (because of pneumonia) fulfilling at least one of the following [15]:

- (1) Hospitalization for 2 or more days in the preceding 90 days.
- (2) Chronic dialysis within 30 days.
- (3) Home wound care.
- (4) Home infusion therapy including antibiotics.
- (5) Immunosuppressive disease and/or therapy (systemic corticosteroids, immunosuppressive drugs).
- (6) Presence of chronic indwelling devices.

Exclusion criteria were as follows: ventilator-associated pneumonia, hospital-acquired pneumonia, and suspected or known aspiration pneumonia [5].

Methods

All the patients studied were subjected to the following:

- (1) Thorough assessment of medical history, with a focus on other comorbidities.
- (2) Full clinical examination (general and local examination).
- (3) Plain chest radiography (posteroanterior and lateral views).

- (4) Routine laboratory investigations:
 - (a) Complete blood picture.
 - (b) Liver functions.
 - (c) Kidney functions.
 - (d) Blood sugar testing.
- (5) The CURB-65 scoring system was used for assessment of severity: ICU admission was considered if patients fulfilled more than two criteria of the CURB-65 scoring system, whereas ward admission was considered if patients fulfilled only two criteria [confusion, blood urea nitrogen >7 mmol/l (Blood urea nitrogen (BUN) >19.6 mg/dl), respiratory rate >30 breaths/min, blood pressure <90 mmHg systolic or <60 mmHg diastolic, age ≥ 65 years] [16].
- (6) Measurement of serum biomarker proADM level was performed in the first 24 h of the admission. Seven milliliter venous blood samples were obtained and collected in tubes containing EDTA. After centrifugation, they were kept frozen at -80°C until assayed. ProADM was measured using the enzyme immunoassay kit, which is designed to detect a specific peptide and its related peptides on the basis of the principle of competitive enzyme immunoassay (DRG International Inc., USA). The normal reference range is 0.33 ± 0.7 nmol/l [17].
- (7) Assessment of duration of hospital stay and occurrence of complication(s), for example, septic shock, acute respiratory distress syndrome (ARDS), empyema, or need for MV.

Septic shock: defined as the presence of systemic inflammatory response syndrome, documented by infection or positive blood culture and organ dysfunction, hypoperfusion, or sepsis-induced hypotension refractory to adequate fluid resuscitation or the use of inotropics or vasopressor support [18].

ARDS: acute onset, bilateral infiltrates on chest radiographs, pulmonary artery occlusion pressure less than 18 mmHg, if measured, or absence of clinical signs of left atrial hypertension, and presence of $\text{PaO}_2/\text{FiO}_2$ less than 200 mmHg [19].
- (8) Assessment of final outcome, which was either discharge or death.

Statistical analysis

Statistical analysis was carried out using the SPSS statistical software package (version 19; SPSS Inc., Chicago, Illinois, USA).

Data were presented as mean \pm SD for quantitative continuous data, comparison between the means of several groups was performed by one-way analysis for variance (*F*-test), and post-hoc analysis (LSD) was carried out.

Table 1 Demographic data of the studied patients

Parameters	HCAP (n = 31)	CAP (n = 25)	P-value
Age (mean ± SD)	64.1 ± 9.8	57.4 ± 10.9	0.02
Sex (male/female)	20/11	15/10	0.70
Current smokers [n (%)]	11 (35.5)	13 (52.0)	0.21
Systolic BP (mean ± SD) (mmHg)	103.2 ± 22.7	115.5 ± 22.3	0.04
Diastolic BP (mean ± SD) (mmHg)	64.03 ± 11.34	73.72 ± 11.85	0.04
Temperature (mean ± SD) (°C)	37.5 ± 1.6	38.6 ± 0.6	0.003
Respiratory rate (breaths/min)	32.7 ± 3.2	30.7 ± 3.1	0.025
Confusion [n (%)]	12 (38.71)	5 (20)	0.046
ICU admission [n (%)]	19 (61.3)	8 (32)	0.03

BP, blood pressure; CAP, community-acquired pneumonia; HCAP, healthcare-associated pneumonia.

Table 2 Risk factors of healthcare-associated pneumonia patients

Risk factors	N (%)
Home wound care	4 (12.9)
Hospitalization for ≥2 days in previous 90 days	12 (38.7)
Immunosuppressive diseases	7 (22.6)
Immunosuppressive therapy	8 (25.8)

Table 3 Laboratory data of the studied groups

Parameters	HCAP (n = 31)	CAP (n = 25)	P-value
WBC (mean ± SD) (×10 ⁹ cells/l)	9.1 ± 3.1	13.75 ± 3.35	0.001
Creatinine (mean ± SD) (mg/dl)	2.1 ± 0.7	0.6 ± 0.3	0.001
BUN (mean ± SD) (mg/dl)	37.8 ± 12	26.3 ± 5.8	0.035
ProADM (mean ± SD) (nmol/l)	3.52 ± 1.0	1.18 ± 0.35	0.001

CAP, community-acquired pneumonia; HCAP, healthcare-associated pneumonia; proADM, proadrenomedullin; WBC, white blood cell.

Table 4 Patients' outcome during hospitalization

Parameters	HCAP (n = 31)	CAP (n = 25)	P-value
Duration of hospital stay (mean ± SD)	17.6 ± 4.8	9.3 ± 3.2	0.001
Occurrence of complications [n (%)]			
Empyema	4 (12.9)	0 (0.0)	–
Septic shock	2 (6.45)	0 (0.0)	–
ARDS	3 (9.67)	0 (0.0)	–
Need for MV	10 (32.25)	2 (8.0)	0.027
Mortality [n (%)]	5 (16.12)	0 (0.0)	–

ARDS, acute respiratory distress syndrome; CAP, community-acquired pneumonia; HCAP, healthcare-associated pneumonia; MV, mechanical ventilation.

Table 5 Comparison between levels of proadrenomedullin (nmol/l) among patients of both groups in the severity of pneumonia (measured by CURB-65)

Pneumonia severity studied groups	CURB-65 score ≤2		CURB-65 score >2		P-value
	N (%)	ProADM (nmol/l)	N (%)	ProADM (nmol/l)	
HCAP (n = 31)	12 (38.71)	2.3 ± 0.5	19 (61.29)	4.3 ± 0.4	0.0001
CAP (n = 25)	17 (68)	0.99 ± 0.21	8 (32)	1.6 ± 0.19	0.0001

CAP, community-acquired pneumonia; HCAP, healthcare-associated pneumonia; proADM, proadrenomedullin.

Qualitative data were presented as number and percentage, and association was tested using the χ^2 -test.

The receiver operating characteristic (ROC) curve was used to predict cut-off values of severity and mortality from HCAP and area under the curve; 95% confidence interval was used. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated, and κ measurement was performed. *P*-value less than 0.05 was considered significant.

Results

Table 1 shows the demographic data of all the patients enrolled in this study. There were statistically significant differences between HCAP and CAP patients in age, blood pressure (systolic and diastolic), temperature, respiratory rate, and presence of confusion. Also, HCAP patients showed higher number of ICU admissions than CAP patients.

Table 2 shows the risk factors of HCAP patients, indicating that hospitalization of 2 or more days in the previous 90 days was the most common risk factor in these patients.

Table 3 shows a statistically highly significant increase in the proADM level (nmol/l) in the HCAP group than that in the CAP group (*P* = 0.001). Also, there was a statistically significant increase in BUN (mg/dl) and creatinine (mg/dl) levels in the HCAP group than that in the CAP group (*P* = 0.035 and 0.001, respectively). However, a statistically highly significant decrease in the white blood cell counts (×10⁹/l) was detected in the HCAP group than in the CAP group (*P* = 0.001).

Table 4 shows the outcome of both groups during hospitalization. Patients with HCAP were significantly more likely to develop complications (empyema, septic shock, ARDS) and more in need of MV with a prolonged duration of hospital stay than patients with CAP (*P* < 0.05). Mortality occurred only in HCAP patients.

Table 5 shows a highly significant increase in the serum level of proADM (nmol/l) on admission with increasing severity of CAP and HCAP assessed by CURB-65 (*P* = 0.0001).

Table 6 shows a statistically significant increase in the serum proADM level (nmol/l) in patients who died than that in survivors in the *HCAP* group ($P = 0.01$).

Figures 1 and 2 show a ROC analysis in which sensitivities were calculated in *HCAP* patients who had severe pneumonia (assessed by the CURB-65 score) and who died during the study. The area under the curve, PPV, NPV, sensitivity, and specificity for cut-off levels of serum proADM (nmol/l) were calculated and are shown in Tables 7 and 8. A serum proADM level more than 1.8 nmol/l had good sensitivity and PPV (91.7% for each), and high specificity and NPV (95% for each) in predicting severe disease among *HCAP*

patients ($P = 0.001$), whereas a serum proADM level more than 2.9 nmol/l had very high sensitivity and NPV (100% for each), but low specificity (42.3%) and low PPV (25%) in predicting mortality among *HCAP* patients ($P = 0.03$).

Discussion

Physicians dealing with patients with pneumonia in the emergency department should be aware that a considerable number of patients presenting with pneumonia may have *HCAP* and require a targeted approach when deciding on empirical antibiotic therapy [1]. Although the PSI and CURB-65 scores are the most widely used predictive scoring systems, each has advantages and limitations. The PSI score has primarily been developed to identify patients with a low risk of mortality who could be treated as outpatients [20]; however, this system can potentially overestimate the severity of illness in elderly patients, especially those with comorbidities. In contrast, the CURB-65 score has been developed to enable easy identification of patients with severe illness with a high mortality risk [21], but it is not ideal for identification of patients with multiple comorbidities [22].

Therefore, there is growing interest in the search for biomarkers enabling improvement in risk stratification alone or in combination with clinical prognostic scores [23]. Previous studies have reported mid-regional proADM) as a promising marker as

Table 6 Serum proadrenomedullin levels (nmol/l) and mortality in the healthcare-associated pneumonia group

Parameter	Survivors in <i>HCAP</i> (n = 26)	Nonsurvivors in <i>HCAP</i> (n = 5)	P-value
ProADM (mean ± SD)	3.34 ± 1.0	4.7 ± 0.02	0.01

HCAP, healthcare-associated pneumonia; proADM, proadrenomedullin.

Table 7 Cut-off levels of proadrenomedullin (nmol/l) in predicting severity and mortality in the healthcare-associated pneumonia group

Parameters	Cut-off level	AUC	95% CI
ProADM level (nmol/l) in severity	>1.8	0.96	0.886–1.037
ProADM level (nmol/l) in mortality	>2.9	1	1–1

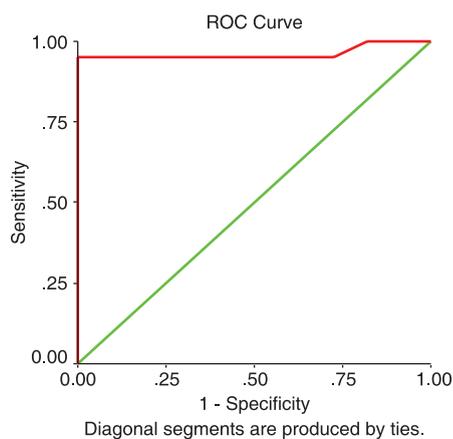
AUC, area under the curve; CI, confidence interval; proADM, proadrenomedullin

Table 8 Sensitivity, specificity, positive predictive value, and negative predictive value at cut-off levels of severity and mortality of serum proadrenomedullin (nmol/l)

Parameters	Sensitivity	Specificity	PPV	NPV	κ	P-value
Severity (>1.8 nmol/l)	91.7	95	91.7	95	0.86 ± 0.17	0.001
Mortality (>2.9 nmol/l)	100	42.3	25	100	0.19 ± 0.1	0.03

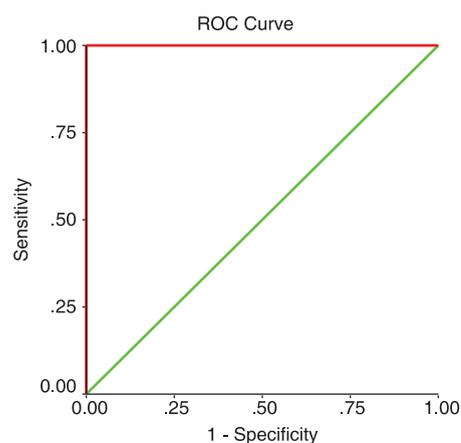
NPV, negative predictive value; PPV, positive predictive value.

Fig. 1



Receiver operating characteristic (ROC) curve for prediction of severity in healthcare-associated pneumonia patients.

Fig. 2



Receiver operating characteristic (ROC) curve for prediction of mortality in healthcare-associated pneumonia patients.

it has multiple tissue sites of action and multiple functions including vasodilatory, anti-inflammatory, and antimicrobial activities [24]. Furthermore, the use of proADM in combination with CURB-65 was found to reduce the initial length of stay compared with the CURB-65 score alone in patients with CAP [25].

Clinical management of HCA represented a major concern as these fragile patients usually show an unusual clinical presentation that frequently misleads severity assessment and results in poor clinical outcomes [4]. Therefore, this study was carried out to evaluate the role of proADM in assessing disease severity and outcome in *HCAP* patients.

In this study, there was a statistically significant increase in age (years) in the *HCAP* group than in the CAP group (Table 1). Similar results were obtained by Kollef *et al.* [26], Carratala *et al.* [1], Polverino and Torres [15], and Attridge *et al.* [3], who reported that the clinical presentation of *HCAP* patients is frequently associated with advanced age, presence of neurological disorders, presence of multiple chronic comorbidities, and/or receiving medicare than patients with CAP.

Also, there were statistically significant differences between the CAP and *HCAP* groups in all parameters of the clinical data (systolic and diastolic blood pressure, temperature, conscious level, and respiratory rate) (Table 1). These results are not in agreement with those of Carratala *et al.* [1] and Polverino and Torres [15], who reported that extrapulmonary manifestations including mental confusion were more frequent in the *HCAP* group. However, Polverino *et al.* [4] observed, from their study, that there was no difference between CAP and *HCAP* patients in the data of clinical presentation.

The current study found a statistically highly significant increase in the serum level of proADM in the *HCAP* group than that in the CAP group (Table 3). Our results were in agreement with those of Polverino *et al.* [4], who reported that serum proADM and procalcitonin were higher in the *HCAP* group than in the CAP group on hospital admission.

For patients' outcome, a statistically highly significant increase was observed in *HCAP* patients than in CAP patients in the duration of hospital stay. Also, there was a statistically significant increase in the development of complications (empyema, septic shock, and ARDS) and need for MV in the *HCAP* group than in the CAP group. Mortality occurred only among *HCAP* patients (Table 4).

Our results are in agreement with the results of Kollef *et al.* [26], Carratala *et al.* [1], Micek *et al.* [2], Carrabba *et al.* [5], and Joong *et al.* [22], who reported that (i) *HCAP* patients also had comorbid conditions (chronic obstructive lung disease, chronic heart disease, cerebrovascular disease, and cancer), leading to increased severity of pneumonia, (ii) increased number of risk factors in the same *HCAP* patients were positively correlated with more exposure to complications and mortality, (iii) underestimation of the *HCAP* pathogen as they were likely to be multidrug-resistant organisms (methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*), and their treatment with an inappropriate initial antibiotic regimen would lead to more complications, increased duration of hospital stay, and higher mortality rate.

In contrast to our results, Attridge *et al.* [3] reported that mortality rates and length of hospital stay were lower for *HCAP* patients. This discrepancy may be because theirs was a retrospective cohort study and critically ill patients were excluded from their study.

In the current study, serum proADM levels increased with increasing severity of the disease in both CAP and *HCAP* groups (when assessed by CURB-65), and this increase was statistically highly significant in both groups (Table 5).

Our results are not in agreement with those of Schuetz *et al.* [12], Albrich *et al.* [16], Rabello *et al.* [27], and Suberviola *et al.* [6]. According to Polverino *et al.* [4], increased levels of biomarkers in *HCAP* patients up to 1 month after admission could reflect worse clinical conditions and poorer outcome of these patients. Also, Christ-Crain *et al.* [28] had explained this increase by different mechanisms; first, as a member of the *Calc* gene family, ADM is widely expressed and extensively synthesized during sepsis. Bacterial endotoxins and proinflammatory cytokines upregulate ADM gene expression in many tissues. Second, decreased clearance by the kidneys may be responsible for the increased level in sepsis. Third, an alternative site of proADM clearance may be the lung, and thus, in infection-related lung injury, impaired removal of proADM from pulmonary circulation results in increased proADM plasma levels.

Also, in our study, proADM levels showed a statistically significant increase in *HCAP* patients who died than that in survivors (Table 6). These higher levels in our study could be attributed to the fact that *HCAP* patients had more complications – for example, septic shock, empyema, and ARDS. Similar results were reported by Christ-Crain *et al.* [29], who found increased proADM levels in

nonsurviving septic patients than in the surviving group. Bello *et al.* [13] explained the relationship between high proADM levels and short-term survival as follows:

- (1) Worse general condition is associated with lower immune function, thereby facilitating the spread of respiratory infection, and
- (2) A more severe infection exacerbates the underlying chronic (cardiovascular or renal) disease of the patients.

To evaluate the potential to predict severity and also death from pneumonia in *HCAP* patients, ROC curves were constructed (Figs 1 and 2).

A serum proADM cut-off level more than 1.8 nmol/l had good sensitivity and PPV (91.7% for each) and high specificity and NPV (95% for each) in predicting severity of the disease among *HCAP* patients. However, a serum proADM cut-off level more than 2.9 nmol/l had very high sensitivity and NPV (100% for each), but low specificity (42.3%) and PPV (25%) in predicting mortality among those patients (Table 8). In agreement with our results, Renaud *et al.* [14] reported a cut-off value of 1.8 nmol/l of proADM in predicting early severe CAP and requirement for ICU admission with a sensitivity of 61.3% and a specificity of 76.9%. Another study carried out by Bello *et al.* [13] reported a lower cut-off level (0.646 and 0.833 nmol/l) of proADM in predicting severity and complications, respectively. This difference can be explained as follows:

- (1) Use of the risk of early admission to ICU score (REA-ICU score) as the scoring system for CAP severity assessment and not CURB-65 scoring, and
- (2) The study included immunocompetent CAP patients and not *HCAP* patients.

In contrast to our results, Christ-Crain *et al.* [28] reported that a lower level of serum proADM (1.8 nmol/l) was the optimal cut-off value to predict short-term mortality with a sensitivity of 80% and a specificity of 72%. This discrepancy may be because of patient selection as CAP patients with cystic fibrosis and severely immunocompromised patients were excluded from this study. However, in our study, a small number of patients with heterogeneous risk factors for *HCAP* were included.

ProADM improved both clinical risk scores and was superior for the prediction of serious complications. The incorporation of a combination of biomarkers reflecting systemic inflammation, endothelial dysfunction, stress, and cardiac function into the clinical risk scores

improved their prognostic accuracy for the prediction of short-term complication rates [12].

Conclusion

HCAP patients show a more complicated in-hospital course of pneumonia, with worse outcome than CAP patients. Use of proADM as a novel biomarker enhances the performance of the CURB-65 scoring system for assessment of CAP and *HCAP* severity. In *HCAP* patients, serum proADM level more than 1.8 nmol/l can predict severity with good sensitivity (91.7%) and high specificity (95%), whereas serum proADM level more than 2.9 nmol/l can predict mortality with very high sensitivity (100%) and low specificity (42.3%).

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Conflicts of interest

There are no conflicts of interest.

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