

Depression's Influence on the Asthma Control Test, Japanese Version

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ABSTRACT

Background: Depression has been linked to poorer asthma control in asthmatic patients. Although the Japanese version of the Asthma Control Test (ACT-J) is frequently used as a simple, practical evaluation tool in clinical care settings in Japan, knowledge regarding its efficacy for assessing asthma control in asthmatic patients with depression is limited. Thus, we retrospectively investigated cut-off values of the ACT-J for well-controlled asthma, and explored depression's influence on the test with a questionnaire survey.

Methods: Data were analyzed on 1,962 adult asthmatic patients who had completed both the ACT-J and the Japanese version of the Patient Health Questionnaire-9 (J-PHQ-9) in 2008 questionnaire survey conducted by the Niigata Asthma Treatment Study Group. Patients were classified into low (LD: J-PHQ-9 score of 0-4) or high depression (HD: J-PHQ-9 score of 5-27) groups. In both groups, the efficacy of the ACT-J was confirmed. We then compared the optimal cut-off points for uncontrolled asthma in both groups by performing a receiver operating characteristic (ROC) analysis, using the original classification referred to the GINA classification as the "true" classification.

Results: Cronbach's alpha in the LD and HD group was 0.808 and 0.740 respectively. In both groups, the subgroup with existence of work absenteeism or frequent attacks during the previous 12 months scored lower on the ACT-J. The area under the curve and optimal cut-off point for patients with LD and HD were 0.821 and 0.846, and 23 and 20 respectively.

Conclusions: The efficacy of the ACT-J was confirmed in depressive patients with asthma. Because asthma control as evaluated with the ACT-J can be worse than actual control under depressive states, physicians should also pay attention to a patient's depressive state at evaluation. Further investigations focus on the association between the ACT-J and depression are required.

KEY WORDS

ACT, asthma, control, depression, PHQ-9

INTRODUCTION

The Global Initiative for Asthma (GINA) guidelines have promoted remarkable improvements in the management of asthma, together with several other guidelines for effective asthma management based on these.¹⁻³ Because of its high prevalence,^{4,6} general physicians play a central role in managing asthma. According to these guidelines—including those of the Japanese Society of Allergy (JSA)—a pulmo-

nary function tests are usually required to manage asthma in addition to identifying symptoms patients have, such as coughing and dyspnea. However, general physicians may find it difficult to perform these tests.^{3,7-9} The Asthma Control Test (ACT) was recently developed to assess asthma control,¹⁰ in which a pulmonary function tests are not needed. Research on the ACT has reported it to be an excellent tool for the evaluation of asthma control,¹¹⁻¹³ and has identified a cut-off score for controlled or uncontrolled

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asthma of 19 or 20 on the test.¹⁴⁻¹⁷ The efficacy of the Japanese version of the ACT (ACT-J), which has been introduced in Japan, has also been verified.¹⁸⁻²⁰ However, few studies have examined the ACT-J's optimal cut-off score for predicting well-controlled or uncontrolled asthma. In a previous study that we conducted, we identified a cut-off score of no lower than 22 on the ACT-J for predicting well-controlled asthma with high specificity and sensitivity.^{21,22} From these results, we speculated that a specific cut-off score could not be fixed, but was variable under different conditions, including ethnicity and complicated diseases.

On the other hand, psychological factors have been found to be associated with asthma.^{23,24} Among these, depression plays an influential role because health-related quality of life, one of the most important goals of asthma management, is reduced by the onset of depression.^{25,26} In secondary care populations, up to 50% of patients with asthma have been reported to have clinically significant depressive symptoms, and over a third of asthmatic outpatients have been known to have a major depressive episode.²⁷⁻³² Large-scale studies identified an age- and sex-adjusted odds ratio of 1.6 for depression in individuals with asthma compared to those without.³³⁻³⁵ The Patient Health Questionnaire-9 (PHQ-9), consisting of nine items related to depression alone, was developed for evaluating depressive states in actual clinical care. Its sensitivity and specificity have been shown to be high compared with other questionnaires for depression.³⁶ A higher score on the PHQ-9 indicates more severe depression. In 2007, the validity of the Japanese version of the PHQ-9 (J-PHQ-9) was confirmed by Muramatsu *et al.*³⁷

The Niigata Asthma Treatment Study Group has been conducting a regular questionnaire survey of problems related to asthma management since 1998. Analyzing survey data from 2008, we reported that depression might worsen asthma control as results indicated that patients with higher PHQ-9 scores also had lower ACT-J scores.³⁸ There are two possible explanations for our findings. The first is that depression actually influences control of asthma. The second is that asthmatic patients with depression may express lower scores on the measure (the ACT-J) than those without depression even when both have the same actual levels of control; depression may alter the optimal cut-off score of the ACT-J for predicting controlled or uncontrolled asthma. In this study, we explored the influence of depression on the cut-off score of the ACT-J for controlled or uncontrolled asthma, referring to the GINA guidelines for our definition of the construct and using data drawn from our 2008 questionnaire survey.

METHODS

Participation in the study was open to all medical in-

stitutions in the Niigata Prefecture if they intended to join the Niigata Asthma Treatment Study Group. This study was performed with the approval of the Ethics Committee at the School of Medicine of Niigata University (#701), Japan, or at participating institutions, in accordance with the Ethical Principles for Medical Research Involving Human Subjects (Declaration of Helsinki). Written informed consent was obtained from all of the patients. The study involved 28 large hospitals (200 beds or more), 14 small hospitals (fewer than 200 beds), and 62 clinics (no beds). We received 3,146 responses from 5,260 questionnaires (response rate: 59.8%). The content of the questionnaire was written in Japanese, and the questionnaire survey was performed over 2 months from September to October 2008. Subjects were adult patients (aged 16 years or more) with bronchial asthma who regularly visited the participating institutions for asthma management (typically once or twice per month). The recruited patients were asked to complete the questionnaire by themselves. Individual patients were therefore expected to understand technical terms such as "attack" in the questionnaire. This questionnaire also included the ACT-J.

In addition to the ACT-J, patients were asked about their peak flow meter (PEFM) use, smoking status, and incidence of asthma attacks during the 2 weeks prior. The questionnaire also included items on asthma-related symptoms over the 2-week period before completing the questionnaire, including those regarding coughs and sputum in the morning and at night, and sleep disturbances. The patients were also asked a series of questions to evaluate their condition during the year before completing the ACT-J questionnaire. In addition to monitoring the completion of the questionnaire by the patient, physicians were asked to supply details on current treatment, medication used for primary control, type of asthma (atopic or non-atopic) as indicated by total serum IgE or detection of a specific IgE for allergens, and severity of asthma in accordance with the JSA guideline, Asthma Prevention and Management Guideline 2006, Japan.

We measured depressive symptoms using the nine-item J-PHQ-9 which was developed from the original PRIME-MD PQ (Patient Questionnaire),^{39,40} and in which the response categories were dichotomous ("yes" or "no").³⁹ The J-PHQ-9 can be used to measure the severity of depressive symptoms, with probable scores on the questionnaire ranging from 0 to 27. Score ranges for levels of depressive symptoms were as follows: minimal (0-4), mild (5-9), moderate (10-14), moderate-severe (15-19), and severe (20-27). In this study, we assessed the J-PHQ-9 scores of participants according to the original PRIME-MD Patient Health Questionnaire (PQ) and divided the scores into the following two groups: the low-grade depressive group (LD: J-PHQ-9 score = 0-4) and high-grade depressive group (HD: J-PHQ-9 score = 5-27).

Based on the questionnaire survey mentioned above, each patient was retrospectively evaluated with respect to the following criteria: (1) the frequency of asthma attacks during the previous 2 weeks before completing the questionnaire, classified as “none,” “1-2 times/week,” “3-4 times/week,” or “5-7 times/week”; (2) the appearance of morning and nocturnal symptoms related to asthma during the previous 2 weeks before completing the questionnaire, classified as “symptom (-)” or “symptom (+)”; (3) the existence of sleep disturbances during the past 2 weeks before completing the questionnaire, classified as “sleep disturbance (-)” or “sleep disturbance (+)”; (4) the existence of work absenteeism during the year before completing the questionnaire, classified as “absent” or “present”; (5) frequency of asthma attacks during the year before completing the questionnaire, classified as “few” “seasonal” or “persistent”; and (6) the severity of asthma based on the 2006 JSA guideline, classified as Step 1, 2, 3, or 4. Patients were divided into groups based on their responses to each category.

Analyses of the influence of depression on the ACT-J were then performed with the following procedure. First, we divided the patients into 2 groups, LD and HD, according to their J-PHQ-9 scores. Cronbach's alpha, an excellent indicator of internal consistency in questionnaires ranged from 0.000 to 1.000, was calculated for both groups. The questionnaire is usually estimated to be reliable when it is beyond 0.700. Second, comparisons of the ACT-J scores were performed among patients with different asthma control levels in LD and HD groups. These steps were performed to determine the reliability and validity of the ACT-J in assessing asthma control in each study group. Because the original aim of conducting the ACT-J in the 2008 survey was not to evaluate the test's efficacy but to assess patients' asthma control, there was inadequate information on exact criteria for establishing asthma control provided by GINA 2006. Thus, status of asthma control, as referred by GINA 2006 guidelines, was determined using criteria (1), (2), and (3) mentioned above: (A) controlled asthma, in which a patient had no asthma attacks, no morning or nocturnal symptoms related to asthma, and no sleep disturbances during the 2 weeks before answering the questionnaire; (B) uncontrolled asthma, in which a patient had asthma attacks, symptoms that included sleep disturbances, or morning or nocturnal symptoms related to asthma during the 2 weeks before completing the questionnaire. Employing this definition, the screening performance of the ACT-J was analyzed to ascertain depression's influence on the ACT-J scores of patients with equivalent control.

Results for continuous variables, except ACT-J and J-PHQ-9 scores, were expressed as arithmetic means and standard deviations. ACT-J and J-PHQ-9 scores were expressed as median values and interquartile

ranges (IQRs). Intergroup differences in terms of continuous variables were evaluated using the Kruskal-Wallis test and Mann-Whitney U test with Bonferroni correction. All statistical analyses were performed using the statistical software JMP® 10 (SAS Institute; Cary, NC, USA) and SPSS. For all statistical analyses, a *P*-value of <0.05 was considered significant.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS

Of the 3,146 asthmatic patients who answered the questionnaire, 1,962 also completed the ACT-J and J-PHQ-9. Demographic and clinical characteristics of the patients are shown in Table 1. The age (years, mean $\pm$ SD), gender (% male/female), disease duration (years, mean $\pm$ SD), disease type (% atopic/non-atopic), smoking status (% non-smoker/ex-smoker/current-smoker), and peak-flow meter use rate (%) were 54.8 ± 17.2 , 42.7/55.9, 14.3 ± 13.9 , 45.7/48.7, 51.3/30.0/16.5, and 26.9 respectively. Median ACT-J and PHQ-9 scores [interquartile range (IQR)] were 23 [20-25] and 1 [0-4], respectively. Rates (%) of asthma attacks, morning symptoms, nocturnal symptoms, and sleep disturbances during the previous 2 weeks before the questionnaire were 24.4, 42.4, 30.2, and 14.1 respectively. The rate of work absenteeism during the previous 12 months before the questionnaire was 9.5%. The proportions (%) of patients who qualified their asthma attacks, responding with “persistent attacks”, “seasonal attacks” and “few attacks,” were 9.8, 36.5 and 45.0%, respectively. The rates of use for each type of medication were: >80% for inhaled corticosteroids (ICS), >40% for leukotriene receptor antagonists (LTRAs), >40% for oral sustained-released theophylline (OSRT), 4.9% for oral corticosteroids (OCS), and 38.9% for long-acting beta agonists (LABAs). The rates (%) of asthma severity (Steps 1 through 4) were 24.2, 39.1, 26.6, and 5.2 respectively. Meanwhile, the rates of “controlled” and “uncontrolled” asthma, as defined by our original classification, were 49.3 and 50.7 respectively.

EFFICACY OF THE ACT-J FOR ASSESSING ASTHMA CONTROL IN LOW- AND HIGH-GRADE DEPRESSIVE GROUPS

Cronbach's alpha in the LD and HD groups was 0.808 and 0.740 respectively. In both groups, ACT-J scores were significantly lower among patients who had experienced work absenteeism due to asthma exacerbations during the year before the questionnaire than those who had not (Table 2A, B). Furthermore, the ACT-J scores of patients with seasonal and persistent attacks were significantly lower than those of patients who experienced few attacks. Patients with persistent attacks scored significantly lower on the test than those with seasonal attacks (Table 3A, B).

Table 1 Demographic and clinical characteristics

Cases	1962
Age (years, mean $\pm$ SD)	54.8 $\pm$ 17.2
Gender (% , male/female)	42.7/55.9
Disease duration (years, mean $\pm$ SD)	14.3 $\pm$ 13.9
Disease type (% , atopic/non-atopic)	45.7/48.7
Smoking status (% , non-smoker/ex-smoker/current smoker)	51.3/30.0/16.5
Peak-flow meter use rate (%)	26.9
ACT-J score (median [IQR])	23 [20-25]
J-PHQ-9 score (median [IQR])	1 [0-4]
Attack rate during the previous 2 weeks before completing the questionnaire (%)	24.4
Morning symptom rate during the previous 2 weeks before completing the questionnaire (%)	42.4
Nocturnal rate during the previous 2 weeks before completing the questionnaire (%)	30.2
Sleep disturbance rate in the previous 2 weeks before completing the questionnaire (%)	14.1
Work absenteeism rate during the previous year before completing the questionnaire (%)	9.5
Frequency of asthma attacks during the previous year before completing the questionnaire (% , frequent/seasonal/few)	9.8/36.7/45.0
ICS use rate (%)	86.4
LTRA use rate (%)	42.6
OSRT use rate (%)	43.4
OCS use rate (%)	4.9
LABA use rate (%)	38.9
Severity of asthma based on the 2006 JSA guideline (% , Step 1/2/3/4)	24.2/39.1/26.6/5.2
“Controlled” asthma rate (%)	49.3
“Uncontrolled” asthma rate (%)	50.7

ACT-J, the Asthma Control Test, Japanese Version; J-PHQ-9, the Japanese version of the Patient Health Questionnaire-9; IQR, inter-quartile range; ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist; OSRT, oral sustained-release theophylline; OCS, oral corticosteroid; LABA, long-acting beta agonist.

“Controlled” asthma and “uncontrolled” asthma are defined according to our original classifications.

Table 2A Comparison of ACT-J scores with regard to work absenteeism during the year before completing the questionnaire (LD group)

	None	Existence of work absenteeism
Number of patients	1400	114
ACT-J score (median [IQR])	24 [21-25]	21 [18-24]*

Table 2B Comparison of ACT-J scores with regard to work absenteeism during the year before completing the questionnaire (HD group)

	None	Existence of work absenteeism
Number of patients	295	72
ACT-J score (median [IQR])	22 [19-24]	18 [13-21]*

ACT-J, the Asthma Control Test, Japanese Version; IQR, inter-quartile range. * $p < 0.0001$.

Table 3A Comparison of ACT-J scores among patients with different asthma attack frequencies during the year before completing the questionnaire (LD group)

	Few attacks	Seasonal attacks	Persistent attacks
Number of patients	757	571	121
ACT-J score (median [IQR])	24 [23-25]	22 [20-24]*	19 [16-21]*, **

Table 3B Comparison of ACT-J scores among patients with different asthma attack frequencies during the year before completing the questionnaire (HD group)

	Few attacks	Seasonal attacks	Persistent attacks
Number of patients	126	150	72
ACT-J score (median [IQR])	23.5 [22-25]	21 [16-23]*	16.5 [11-19]*, **

ACT-J, the Asthma Control Test, Japanese Version; IQR, inter-quartile range. * $p < 0.0005$ vs. few; ** $p < 0.0005$ vs. seasonal.

Table 4A Screening performance of the ACT-J for LD group at different cut-off points

ACT-J score/ cut-off point	Sensitivity, %	Specificity, %	Positive predic- tive value, %	Negative predic- tive value, %	Youden index	Area under the curve
15	10.69	99.40	94.04	55.82	0.101	0.551
16	13.94	99.28	94.49	56.70	0.132	0.566
17	18.81	98.93	93.91	58.04	0.177	0.589
18	23.82	98.57	93.61	59.75	0.224	0.612
19	32.61	97.97	93.41	62.27	0.306	0.653
20	44.65	95.71	90.16	66.25	0.446	0.702
21	54.67	92.01	82.77	69.73	0.467	0.733
22	65.09	83.67	77.83	73.12	0.488	0.744
23	78.35	73.60	72.28	79.40	0.519	0.760
24	90.26	44.34	58.81	83.78	0.346	0.673

Table 4B Screening performance of the ACT-J for HD group at different cut-off points

ACT-J score/ cut-off point	Sensitivity, %	Specificity, %	Positive predic- tive value, %	Negative predic- tive value, %	Youden index	Area under the curve
18	43.19	99.21	99.10	46.32	0.424	0.712
19	52.14	94.49	95.03	49.38	0.466	0.733
20	61.09	92.13	94.01	53.91	0.532	0.766
21	70.43	82.20	88.29	57.54	0.515	0.763
22	78.21	67.72	83.05	60.56	0.459	0.730
23	89.88	59.06	81.62	74.25	0.489	0.745
24	95.33	36.22	75.15	79.31	0.316	0.658

SCREENING ACCURACY AND DETERMINATION OF OPTIMAL ACT-J CUT-OFF POINT

The accuracy of the ACT-J in screening for uncontrolled asthma in the LD group is summarized in Table 4A, where the ACT-J scores represent different proposed cut-off points. Cut-off points <14 yielded poor ACT-J classification accuracy and were therefore dismissed. A score of 23, however, saw the Youden index peak at 0.519, the maximum. Consequently, we used an ACT-J score of 23 as the optimal cut-off point for predicting uncontrolled asthma in the LD group. As seen from the ROC curve, a cut-off point of 23 represented the point closest to the top left corner; the area under the curve (AUC) was 0.821 (Fig. 1A).

The performance of the ACT-J in screening for uncontrolled asthma among patients in the HD group is summarized in Table 4B, where the ACT-J scores represent different proposed cut-off points. Cut-off points <10 yielded poor ACT-J classification accuracy and were therefore dismissed. A score of 20 instead saw the Youden index reach a maximum of 0.532. Therefore, we used an ACT-J score of 20 as the optimal cut-off point for predicting uncontrolled asthma in the HD group. As Figure 1B illustrates, a cut-off point of 20 represented the point closest to the top left corner of the ROC curve, and the AUC was 0.846.

DISCUSSION

We have previously reported that the cut-off score of

the ACT-J for GINA-defined asthma control differed from those for other populations.²² This indicates the probability that the cut-off may be partially influenced by a variety of factors, including depression. The aim of this study was to investigate the influence of depression on the ACT-J, especially on its cut-off score, using a questionnaire survey.

To achieve this aim, it was necessary to confirm the efficacy of the ACT-J for use with asthmatic patients who not only had low-grade but also high-grade depression. As mentioned before, the test's Cronbach's alpha was computed for LD and HD groups of participants and found to be beyond 0.700 in both instances. In both groups, as well, the ACT-J scores of subgroups that we had expected to be low, such as those of patients with persistent asthmatic symptoms, were actually lower than for patients in opposite subgroups whose scores we had anticipated would be high (Table 2A, B, 3A, B). These results clearly show that survey data obtained with the ACT-J on both LD and HD groups had acceptable reliability and validity. Additionally, the ROC curves of the ACT-J generated for both groups (Fig. 1A, B) identified a lower optimal cut-off score for the HD group than for the LD group. This suggests that an asthmatic patient can be evaluated as having worse asthma control with the ACT-J when in a more depressive state. In managing asthma in depressive patients, more objective methods for evaluating asthma control, such as peak-flow meter

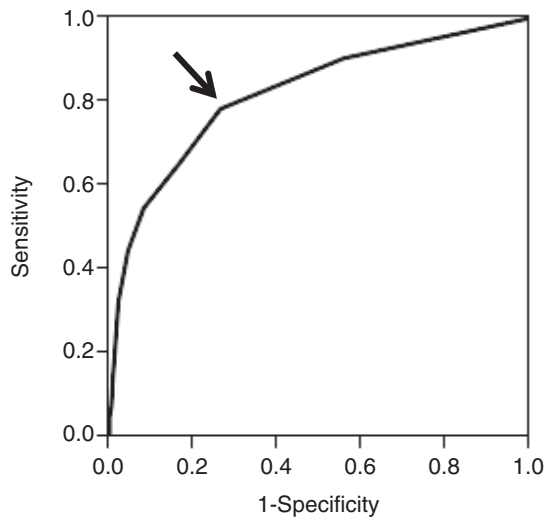


Fig. 1A ROC curve of the ACT-J score for assessing uncontrolled asthma in LD group. The area under the curve (AUC) was 0.821 (95% CI: 0.801-0.843), and the optimal cut-off point was 23.

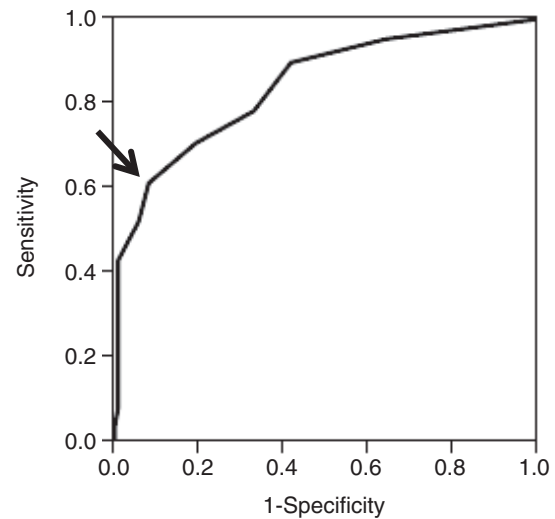


Fig. 1B ROC curve of the ACT-J score for assessing uncontrolled asthma in HD group. The area under the curve (AUC) was 0.846 (95% CI: 0.807-0.885), and the optimal cut-off point was 20.

use, are needed. Some clinicians are naturally likely to realize the effects of depressive states on asthma control due to their vast experience in managing the condition in their patients. However, more objective data regarding the evaluation of asthma control in depressive patients using the ACT were not available until now. Our report is thought to be the first to address this point with regard to asthma control screening.

The reason why ACT-J scores are lower in depressive patients is partly because an objective measure of asthma control, such as a pulmonary function test, is excluded from the ACT-J. In our previous study, we speculated that differences in the ACT's optimal cut-off scores for Japanese and non-Japanese patients could stem from a difference in how symptoms of asthma are perceived and expressed.²² The intensity of dyspnea as experienced by individuals with asthma does not correlate well with their degrees of airway obstruction as determined by spirometry.^{41,42} While patients with stable asthma always experience dyspnea after inhalation of a bronchoconstrictive agent, the degree of dyspnea associated with any fixed decline (e.g., 20%) in the forced expiratory volume in 1 second during peak expiratory flow varies widely.⁴³ Somatosensory amplification has recently been introduced as a probable explanation for the dissociation between subjective and objective symptoms in various diseases.^{44,45} Somatosensory amplification has been reported as playing an important role in patients with asthma.⁴⁶ Further investigation, such as depression-dependent differences in somatosensory amplification, might be required to explain the different cut-off points of the ACT-J.

There were several limitations in this study. The first pertained to the definition of asthma control used in the study. The definition of true asthma control used for generating ROC curves for analyses was based on different items measuring asthma control in the ACT-J and not entirely on the GINA guidelines. Therefore, the absolute value of the cut-off score demonstrated in the present study was insufficient with regard to GINA-defined control of asthma. An important and meaningful finding, however, was the existence of a significant difference in optimal cut-off points between LD and HD groups of patients. The second limitation was the study's use of the J-PHQ-9. Although the questionnaire is a useful screening tool for depressive disorder, the study population may have also comprised patients who had mood disorders other than depression (e.g., anxiety or adjustment disorders) and those who could not be diagnosed as having depression according to DSM-IV criteria, usually used by trained psychologists, but who were mildly depressed. Further confirmation of our results using definition criteria based entirely on GINA 2006 guidelines and other evaluation methods for depression is necessary.

In summary, we confirmed the efficacy of the ACT-J for assessing asthma control in asthmatics with more severe depression. However, the cut-off point of the ACT-J in more depressive patients was obviously lower than that in less depressive patients, indicating that physicians should pay attention to a patient's depressive state at evaluation. Further research clarifying the relationship between depression and the ACT-J is needed.

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