Racial Variations in the Incidence of Severe Alcohol Withdrawal

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ABSTRACT

The use of race as a risk assessment tool and pharmacologic target has garnered recent attention and debate. It is currently unclear if a relationship between race and the development of severe alcohol withdrawal exists. We explored this potential relationship using several study groups.

Methods: A simultaneous prospective enrollment of patients and retrospective chart review of severe alcohol withdrawal in two separate settings was performed comparing both the incidence of withdrawal and alcoholism based on race. These two study groups were then compared to an "at risk" group of alcoholics and the general ED population to determine differences in the distribution of race.

Results: Individuals of white race in both study groups were at increased odds [OR 1.93 (CI 1.11–3.39) and 2.19 (CI 1.41–3.40)] of having severe alcohol withdrawal when compared to non-White "at risk" alcoholics. Blacks in both study groups however, appear to have lower odds [OR 0.23 (CI 0.11–0.47) and 0.11 (CI 0.05–0.23)] of having severe alcohol withdrawal when compared to non-Black "at risk" alcoholics.

Conclusions: Despite the controversial use of race in medical research and targeting therapies, there appears to be a difference in the odds of severe alcohol withdrawal based on race. The reasons for this finding are currently unclear.

INTRODUCTION

Almost 8% of Americans meet the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria for alcoholism [1]. These individuals may develop physical dependence and tolerance that is mediated through downregulation of the $GABA_A$ [2,3] and upregulation of N-methyl-D-aspartate (NMDA) receptors [4]. They are at risk for alcohol withdrawal following either a cessation or a reduction in their alcohol intake, the clinical manifestations of which are well characterized. The seminal observational work by Victor and Adams in the 1953 described several independent withdrawal syndromes including alcoholic tremulousness, alcoholic hallucinosis, alcohol withdrawal seizures, and delirium tremens [5]. Delirium tremens is the most dangerous of the alcohol withdrawal syndromes, since it is still accompanied by significant morbidity and mortality [6].

Despite intensive study, it remains unclear which alcohol-dependent patients will develop delirium tremens, and why some

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patients develop no withdrawal syndrome at all. This extremely variable response increases the complexity of risk-stratifying patients for the likelihood of developing severe alcohol withdrawal. A more refined risk assessment might improve utilization of both inpatient and outpatient detoxification services.

Recent advances in genetic mapping and phenotyping have linked alcoholism to familial inheritance and genetic polymorphism in the metabolism of alcohol [7]. Genetic susceptibility to alcohol abuse appears to exist and may be related to variability of central neurotransmitter pathways that regulate pleasure and reward. Despite efforts to understand the genetic risk factors associated with alcoholism, genetic factors associated with the development of alcohol withdrawal and delirium tremens have not been investigated. Our clinical experience strongly suggests that there are profound racial distinctions in the alcohol-withdrawal population, implying that a genetic basis may be underlying this difference. We sought to review our patient population to define the racial differences in the demographics of severe alcohol withdrawal.

STUDY DESIGN

The study setting is a large urban medical center with >700 inpatient beds and 90,000 emergency department (ED) visits annually. More than 80% of hospital admissions originate from the ED. A simultaneous prospective enrollment (Group 1) and retrospective chart review (Group 2) provided the study groups. These 2 groups were compared to 2 separate groups: an "at risk" for alcohol withdrawal group (historical data) (Group 3) and the general racial demographics of all ED patients (provided through an internal review) (Group 4).

For the purposes of this investigation, severe alcohol withdrawal is defined to be present in any patient who required either an intensive care unit (ICU) admission for the management of alcohol withdrawal or high benzodiazepine dosing (defined as requiring >200 mg of intravenous diazepam in less than a 24-hour period) [8].

Four groups were used for demographic comparison:

- Group 1 patients were obtained from a log of all ICU admissions during the period of 2002 to 2003. These years were selected due to the existence of a concurrent prospective ICU study of alcohol withdrawal care [6].
- Group 2 patients were obtained from a retrospective chart search of all medical toxicology consultations from 1999 to 2003 for patients with severe alcohol withdrawal (as defined above). Although not by policy, it is the routine practice in our institution to consult the medical toxicology service on all cases of severe alcohol withdrawal. The patients included in Group 2 were typically admitted to "step-down" units, whereas those admitted directly to the ICU were excluded from this group but may have been in Group 1.
- Group 3 patients were obtained from a prospective study of ED patients who were identified during a 2-month period as "at risk" for alcohol withdrawal by their affirmative response to 2 or more CAGE questionnaire items [9], thus defining themselves as alcoholics [10,11].
- Group 4 served as a general control for hospital demographics and included all adult ED patients who presented during a 6-month period in 2003. These patient demographics were available through a concurrent internal review.

Patient demographic data was analyzed from several perspectives. Race classifications were defined as "White," "Black," "Hispanic," and "Other." "Non-white" is defined as a patient falling into the category of Black, Hispanic, or Other. "Non-Black" is defined as a patient falling into the category of White, Hispanic, or Other. Similarly, "non-Other" is defined as Black, White, or Hispanic. The "Other" category included all non-Black, non-White, and non-Hispanic individuals (e.g., Asian). Cases were excluded if race was not noted in the medical record. Only the initial visit was included if duplicate enrollments occurred due to recurrent hospital visits. Race was either self-labeled by the patient or assigned from the staff when the patient was unable to speak.

Whites in Groups 1 and 2 were compared to non-Whites (*Figures 1A and 2A*) and Blacks in Group 1 and 2 were compared to non-Blacks (*Figures 1B and 2B*). The odds of having severe alcohol withdrawal were determined using Group 3 as the comparison group representing the racial breakdown of the population "at risk." Additionally, we compared Group 3 to Group 4 to determine the odds of meeting CAGE criteria for alcoholism based on race with Group 4 serving as a control for our general population (*Figure 3*).

Odds ratios (OR) and 95% confidence intervals (CI) were calculated via SPSS v. 13, and $p<0.05$ was considered statistically significant. This study was approved by the Institutional Review Board and received exempt status for written consent. Authors from the two prospective studies [6,9] supplied unlinked summary data for analysis.

RESULTS

Group 1

The prospective ICU cohort was comprised of 56 patients with severe alcohol withdrawal. Their racial distribution was as follows: White, 24 (42.86%); Black, 9 (16.07%); Hispanic, 17 (30.36%); and Other, 6 (10.71%) (*Table 1*).

Group 2

The retrospective medical toxicology service consults consisted of 96 patients with severe alcohol withdrawal who were not admitted to the ICU. Their racial distribution was as follows: White, 44 (45.83%); Black, 8 (8.33%); Hispanic, 33 (34.38%); and Other, 11 (11.46%) (see *Table 1*).

Group 3

The prospective ED cohort consisted of 577 patients who answered affirmatively to 2 or more CAGE questionnaire items. Their racial

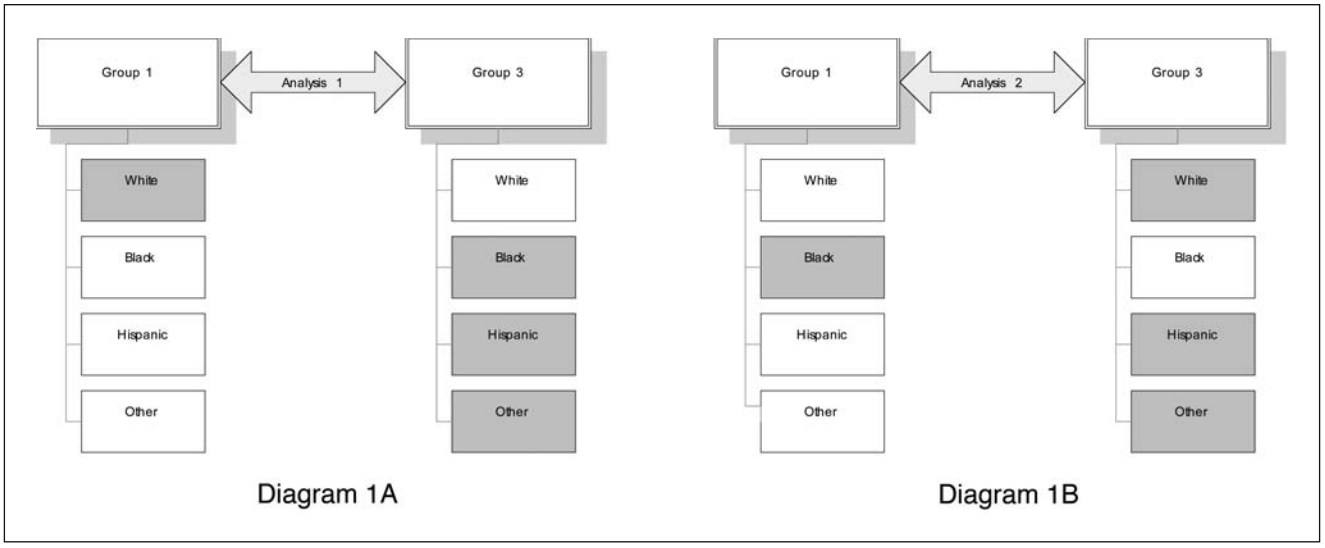

Figure 1: White (1A) and black (1B) ICU patients with alcohol withdrawal compared to non-White (1A) and non-Black (1B) ED alcoholics, respectively.

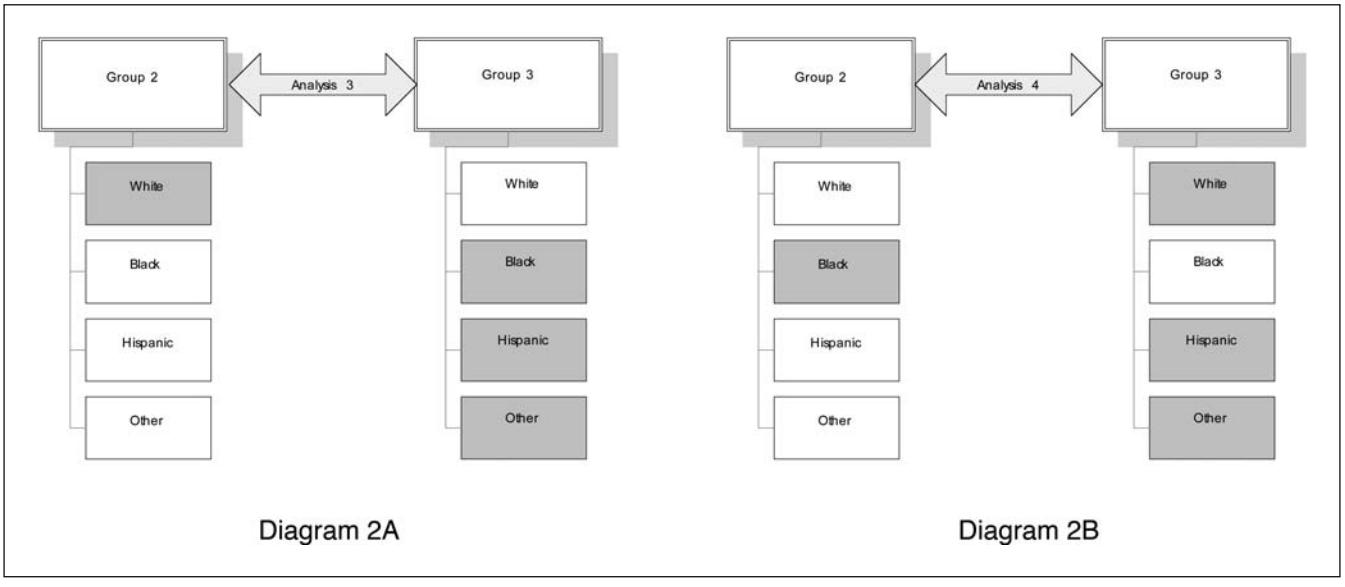

Figure 2: White (2A) and Black (2B) non-ICU patients requiring high benzodiazepine dosing for alcohol withdrawal compared to non-White (2A) and non-Black (2B) ED alcoholics, respectively.

distribution was as follows: White, 161 (27.90%); Black, 264 (45.75%); Hispanic, 137 (23.74%); and Other, 15 (2.60%) (see *Table 1*).

Group 4

The retrospective internal review of all adult ED patients yielded a total of 37,384 patients. Their racial distribution was as follows: White, 7,852 (19.25%); Black, 10,102 (24.77%); Hispanic, 14,645 (35.91%); and Other, 4,785 (20.07%) (see *Table 1*).

There were 7 patients total with recurrent admissions in either Group 1 and Group 2. Only the initial admission was included for analysis. No patients were excluded for lack of racial identifiers in their records.

The following results are summarized in *Table 2*.

White versus non-White

When White patients in Group 1 were compared to non-White patients in Group 3 (see *Figure 1A*), Whites had almost twice the odds [OR, 1.93 (CI, 1.11–3.39)] (see *Table 2*) of having severe alcohol withdrawal. Likewise, White patients in Group 2 had a similar increase in odds [OR, 2.19 (CI, 1.41–3.40)] of having severe

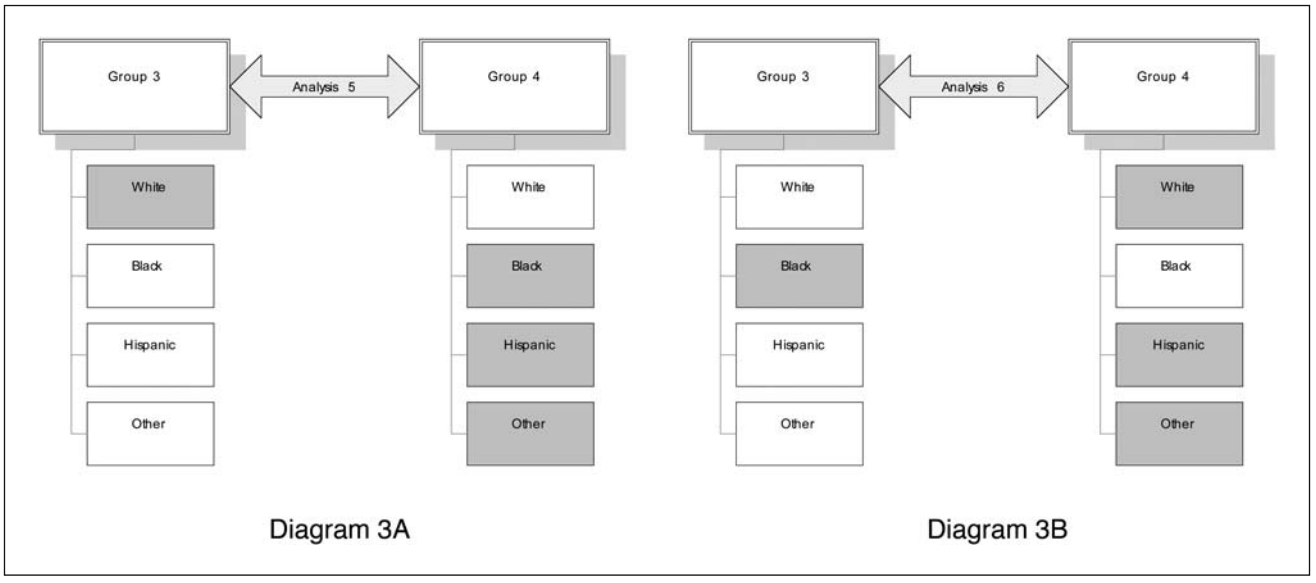

Figure 3: White (3A) and Black (3B) ED patients at risk for alcohol withdrawal by CAGE criteria compared to non-White (3A) and non-Black (3B) ED patients, respectively.

Table 1: Racial Distribution Among Study Groups

	Group 1 ICU patients with alcohol withdrawal	Group 2 Non-ICU patients with high benzodiazepine dosing for alcohol withdrawal	Group 3 ED patients at risk for alcohol withdrawal by CAGE criteria	Group 4 All ED patients
White	24 (42.86%)	44 (45.83%)	161 (27.90%)	7,852 (19.25%)
Black	9 (16.07%)	8 (8.33%)	264 (45.75%)	10,102 (24.77%)
Hispanic	17 (30.36%)	33 (34.38%)	137 (23.74%)	14,645 (35.91%)
Other	6 (10.71%)	11 (11.46%)	15 (2.60%)	4,785 (20.07%)

Table 2: Odds Ratios Among Groups

Comparison	Group 1 vs. Group 3 OR (CI)	Group 2 vs. Group 3 OR (CI)	Group 1 vs. Group 4 OR (CI)	Group 2 vs. Group 4 OR (CI)	Group 3 vs. Group 4 OR (CI)
White vs. nonwhite	1.93 (1.11–3.39)	2.19 (1.41–3.40)	2.82 (1.66–4.79)	3.18 (2.13–4.76)	1.46 (1.21–1.75)
Black vs. nonblack	0.23 (0.11–0.47)	0.11 (0.05–0.23)	0.52 (0.25–1.06)	0.25 (0.12–0.51)	2.28 (1.93–2.69)
Hispanic vs. non-Hispanic	1.40 (0.77–2.55)	1.68 (1.06–2.67)	0.68 (0.38–1.20)	0.81 (0.53–1.24)	0.48 (0.40–0.59)
Other vs. non-Other	4.50 (1.67–12.10)	4.85 (2.16–10.91)	0.82 (0.35–1.91)	0.88 (0.47–1.65)	0.18 (0.19–0.30)

Group 1: ICU patients with alcohol withdrawal
Group 2: Non-ICU high benzodiazepine dosing for alcohol withdrawal
Group 3: ED patients at risk for alcohol withdrawal by CAGE criteria
Group 4: All ED patients
OR: Odds Ratio
CI: 95% Confidence Interval

alcohol withdrawal compared to non-White patients in Group 3 (see *Figure 2A*).

Blacks versus non-Blacks

When Black patients in Group 1 were compared to non-Black patients in Group 3 (see *Figure 1B*), Blacks had lower odds [OR, 0.23 (CI, 0.11–0.47)] of having severe alcohol withdrawal. Likewise, when Black patients in Group 2 were compared to non-Black patients in Group 3 (see *Figure 2B*), there was also a lower odds [OR, 0.11 (CI, 0.05–0.23)] of having severe alcohol withdrawal.

When comparing those ED patients with 2 or more affirmative CAGE responses (Group 3) to all ED patients (Group 4) (see *Figures 3A* and *3B*), Black patients at increased odds [OR, 2.28 (CI, 1.93–2.69)] (see Table 2) to have met CAGE criteria for alcoholism. Despite this, Blacks appeared to have a lower odds (OR, 0.23 and 0.11) of severe alcohol withdrawal when compared to non-Blacks.

DISCUSSION

This retrospective chart review demonstrates an association between White race and increased odds of having severe alcohol withdrawal. Based on these data, White patients have twice the odds of having severe alcohol withdrawal when compared to non-White patients, and Black patients have smaller odds of having severe alcohol withdrawal when compared to non-Black patients. Moreover, while Black patients had decreased odds of having severe alcohol withdrawal, this group had a greater percentage who met CAGE criteria for alcoholism.

The reasons for these findings may be varied, independent, or interdependent. First, genetic variations in ethanol metabolism are demonstrated in certain ethnic groups. For example, in Asians, altered alcohol and aldehyde dehydrogenase enzymes result in the accumulation of acetaldehyde. This results in the nausea, vomiting, and flushing, known as "Asian-flush," that is analogous to a disulfiram reaction [12]. However, this mechanism cannot be implicated as the predominant explanation for the differences in Black and White drinking patterns, tolerance, and withdrawal. Additionally, there appears to be an association with alcoholism and having the haplotype H6 encoding the CYP2E1 isoenzyme in Mexican Americans [13]. It is unclear if this mechanism can be linked to the findings in this study.

The Collaborative Study on the Genetics of Alcoholism (COGA) has identified chromosome linkage of phenotypic traits of alcohol dependence, heavy consumption, and those who are "unaffected" by alcohol to chromosomes 1 and 4 [14]. Interestingly, other research has shown that the GABRA2 gene, which codes for $GABA_A$ subunit, is located on chromosome 4 on a gene cluster that is near to the genes implicated in alcoholic traits [15]. Downregulation of the $GABA_A$ receptor is thought to be the primary physiological change in developing alcohol withdrawal [2,3]. Although there is a genetic proximity of genes that encode alcoholic traits and the $GABA_A$ subunit, there has not been a demonstrated association between the 2 genes.

Differences in alcohol use among racial groups have also been reported. In the overall population the prevalence of alcohol dependence is higher in Whites (5.1%) than in Blacks (3.29%) [1]. Similar differences can be found in binge-drinking patterns: 14.7% of Whites and 9.8% of Blacks [16]. Furthermore, Black patients have less "heavy drinking" patterns when compared to Whites [17]. If alcohol dependence and problem drinking patterns are greater in the White population, it may be reasonable to conclude that Whites have a higher risk of alcohol withdrawal as well. However, this is not the case in our population, in which a higher percentage of Blacks met diagnostic (CAGE) criteria for alcoholism than Whites.

Based on the CAGE criteria, both Black and White patients in our ED had increased odds of alcoholism compared with the Hispanic and Other groups. The CAGE questionnaire is a validated screening tool for alcoholism [10,11]. An affirmative answer to 2 or more of the 4 questions is considered a sensitive screen for alcoholism [11]. It is currently unclear if this questionnaire provides any bias within cultural, ethnic, or racial groups. Assuming not, one may conclude that these patients are "at risk" for developing alcohol withdrawal syndromes. However, in this study, despite having increased odds (OR, 2.28) of alcoholism, Blacks were at lower odds (OR, 0.23 and 0.02) of developing severe alcohol withdrawal when compared to non-Blacks (see *Table 2*).

Alcohol use and dependence may be linked to cultural practices and not necessarily racial/genetic differences. Cultural norms can dictate drinking patterns that are permissible and accepted [18], and this social control may explain the discrepancies found in our data. Self-reporting studies demonstrate that Blacks and Hispanics have more conservative views of drinking norms [19], which may explain a lower prevalence of alcoholism in this group.

Recently, racial distinctions have been brought to the forefront of medical research. Many views have been presented to express both support [20,21] and concern [22] for the use of race in the provision of medical care. Despite a taboo of utilizing race as a risk for illness or a response to therapy, there exists a difference in the quality of care rendered to a patient population that may be racially biased [23]. Our study subjects had either self reported their race or had a race identifier given to them by clerical staff in the ED. The phenotypic expressions of skin color, hair texture, and eye color account for a minute amount of the entire human genome, but our society has and continues to maintain a remarkable focus on these characteristics. Clinicians and scientists, however, seek to discover whether small differences in the genome can account for medical susceptibility and response to pharmacotherapy.

Regardless of any social debate, there are well-established relationships between genetic coding and disease, such as sickle cell anemia, thalassemias, and BRCA (a breast cancer marker) positivity. Additionally, pharmacogenomic therapeutics is at the earliest stages of genetically specified treatments, which may bolster the rationale for profiling patients. Despite these controversies and the early use of pharmacogenomics, there exists a potential

relationship between severity of alcohol withdrawal and race that is not well understood.

LIMITATIONS

This study is based on the combination of 2 prospective and 1 retrospective evaluation utilizing surrogates for severe alcohol withdrawal and a historic control in the same hospital's population. The use of surrogate markers for severity of alcohol withdrawal, such as ICU admission and benzodiazepine requirements, may incorporate a bias based on which patients get admitted to the ICU and receive aggressive therapy. It is possible that these results suggest different treatment practices based on race, either intentionally or unintentionally; we believe this is unlikely due to the motivation of enrollment into the prospective study [6] and the large and ethnically diverse clinical staff who treat these patients. However, presumably unintentional racial bias in medical care and referrals appears to exist in other areas of medicine [24,25].

Using Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA) or other objective measurement would be preferable, but this was not routinely performed at the time of the study. Race identification may be subjective, leading to misclassification. There may be gradations of racial labels between Black and Hispanic, White and Hispanic and Black and White, but this was a task routinely performed by hospital clerical personnel. There was no knowledge at the time of race assignment that it would be used for clinical research, limiting the risk of assignment bias. Furthermore, the "Other" category is not a well-represented cohort in this study, limiting conclusions that can be drawn from this group. The comparison groups (Groups 3 and 4) were not specifically matched with the cases (Groups 1 and 2), but were rather used in their entirety. Whether they are truly comparable is not known.

CONCLUSIONS

Despite the data suggesting that in our study population Whites have a lower rate of alcoholism than Blacks, Whites have greater odds of severe alcohol withdrawal than Blacks, Hispanics, or Others. The reasons for this "racial disparity" are unclear at this time.

The authors have no potential financial conflicts of interest to report.

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