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Thiamine Supplementation in Patients With Alcohol Use Disorder Presenting With Acute Critical Illness

A Nationwide Retrospective Observational Study

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Background: Thiamine supplementation is recommended for patients with alcohol use disorder (AUD). The authors hypothesize that critically ill patients with AUD are commonly not given thiamine supplementation.

Objective: To describe thiamine supplementation incidence in patients with AUD and various critical illnesses (alcohol withdrawal, septic shock, traumatic brain injury [TBI], and diabetic ketoacidosis [DKA]) in the United States.

Design: Retrospective observational study.

Setting: Cerner Health Facts database.

Patients: Adult patients with a diagnosis of AUD who were admitted to the intensive care unit with alcohol withdrawal, septic shock, TBI, or DKA between 2010 and 2017.

Measurements: Incidence and predicted probability of thiamine supplementation in alcohol withdrawal and other critical illnesses.

Results: The study included 14 998 patients with AUD. Mean age was 52.2 years, 77% of participants were male, and in-hospital mortality was 9%. Overall, 7689 patients (51%) received thiamine supplementation. The incidence of thiamine supplementation was 59% for alcohol withdrawal, 26% for septic shock, 41% for TBI, and 24% for DKA. Most of those receiving thiamine (n = 3957 [52%]) received it within 12 hours of presentation in the emergency department. The predominant route of thiamine administration was enteral (n = 3119 [41%]).

Limitation: Specific dosing and duration were not completely captured.

Conclusion: Thiamine supplementation was not provided to almost half of all patients with AUD, raising a quality-of-care issue for this cohort. Supplementation was numerically less frequent in patients with septic shock, DKA, or TBI than in those with alcohol withdrawal. These data will be important for the design of quality improvement studies in critically ill patients with AUD.

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Thiamine deficiency can lead to Wernicke–Korsakoff syndrome (WKS) (that is, the spectrum of Wernicke encephalopathy and Korsakoff syndrome) and beriberi. Untreated thiamine deficiency has been reported as the cause of death in 20% of patients with Wernicke encephalopathy, and irreversible neurologic damage in 85% (1–4). The main treatment of WKS is thiamine replacement, which is generally well tolerated and safe (5, 6). Alcohol use is the most common risk factor for thiamine deficiency in North America, Europe, and Australia (3, 6–8), and patients with septic shock, traumatic brain injury (TBI), and diabetic ketoacidosis (DKA) have also been shown to be at risk (9–13). Thus, it is possible that critically ill patients with alcohol use disorder (AUD) are especially at risk for thiamine deficiency and would benefit from thiamine supplementation.

Many guidelines recommend treatment with thiamine in AUD and alcohol withdrawal to prevent WKS (2, 5, 6, 14). However, limited data are available on how many critically ill patients with AUD actually receive thiamine supplementation. Two previous studies have given different estimates, both of which were relatively low. In 1 single-center pilot study evaluating the practice pattern of thiamine supplementation in patients with AUD presenting with septic shock, only 64% of patients received thiamine (15). The majority (84%) of these patients received the first dose of thiamine in the intensive care unit (ICU), suggesting a potential missed opportunity to administer thiamine earlier in the emergency department (ED). A separate study (9) showed that only 21% of patients with AUD presenting with TBI received thiamine during their hospital stay. The particularly low rate of thiamine repletion reported in TBI raises the possibility that critical illness (apart from just alcohol withdrawal) distracts clinician attention away from the underlying AUD and need for the provision of thiamine.

In our study, we hypothesized that use of thiamine supplementation in critically ill patients with AUD is low.

Methods

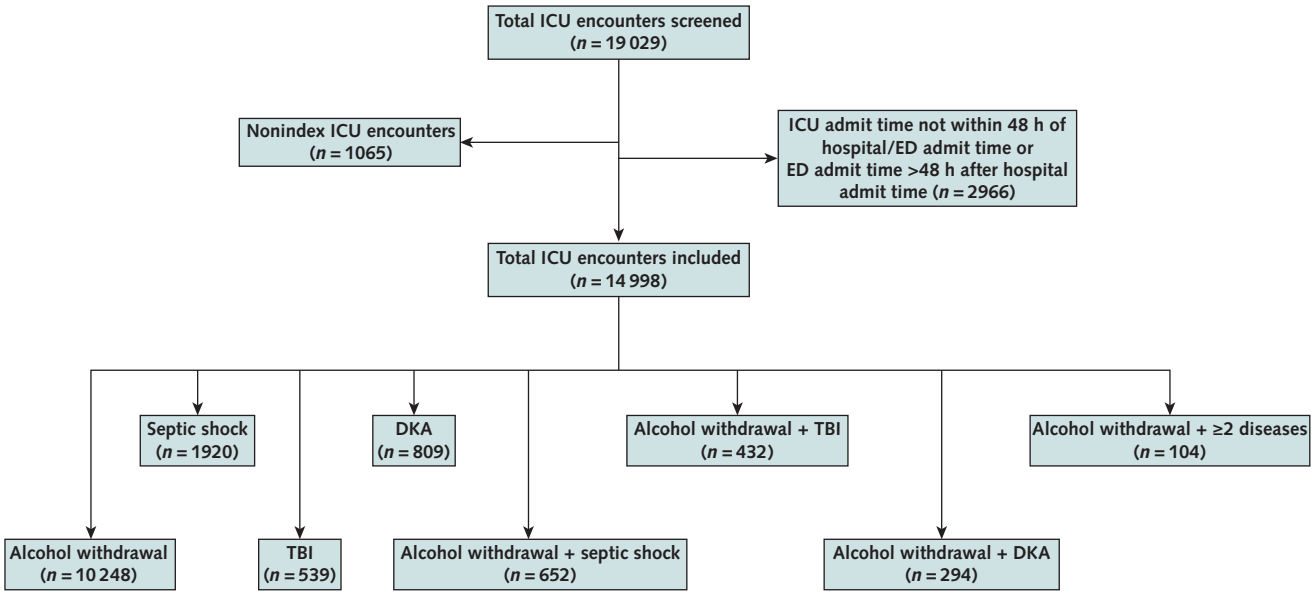
Study Design and Data Source

This was a retrospective observational study using the Cerner Health Facts database, a large, multicenter, and nationally representative data set in the United States. This database complies with the Health Insurance Portability

See also:

Web-Only
Supplement

Figure. Study flow diagram.



DKA = diabetic ketoacidosis; ED = emergency department; ICU = intensive care unit; TBI = traumatic brain injury.

and Accountability Act and stores deidentified electronic health record data generated from Cerner and non-Cerner contributing facilities to facilitate analysis and reporting (16). Encounter-level data (information about encounter type, medications, diagnoses, laboratory orders, and results), hospital characteristics (setting, location, and size), patient characteristics (demographics, comorbid conditions, and disposition), and year of treatment were abstracted. This study was categorized as exempt by the institutional review board at Beth Israel Deaconess Medical Center given the deidentified nature of the database used.

Patient Population

We included adult patients (aged >17 years at the time of admission) who were directly admitted to the ICU from the ED between 2010 and 2017; had International Classification of Diseases, Ninth Revision (ICD-9) or 10th revision (ICD-10), codes for AUD or AUD-attributable conditions (17); and had at least 1 ICD-9 or ICD-10 code for any of the following conditions: alcohol withdrawal, septic shock, TBI, or DKA (the **Supplement Table** [available at Annals.org] provides the ICD-9 and ICD-10 codes). Previous studies have shown that administrative codes (that is, ICD-9 and ICD-10 codes) have high positive predictive value for the diagnosis of AUD (18, 19), and we have validated this approach in our own pilot study (15), which found that use of ICD-9 and ICD-10 codes had a positive predictive value of 98.1% when assessed by manual review of medical records. Patients who had an ICU encounter without a corresponding ED encounter were considered to be direct admissions and were excluded because whether they had received thiamine at another hospital was unknown. Only the index ICU encounter was considered, and ICU encounters from subsequent admissions were excluded. Patients were considered to have received thiamine if they received any dose of thiamine via any route of administration–that is, oral, feeding tube, or intravenous–based on medication codes (**Supplement Table**). Thiamine is sometimes administered jointly with other vitamins in a premixed solution prepared by a pharmacist. However, because this solution is compounded in the pharmacy, individual components, including thiamine, are separately identifiable. Other exclusion criteria were ICU admission time not within 48 hours of ED admission or hospital admission, ED admission time more than 48 hours after hospital admission, and documented time of thiamine administration either more than 48 hours before ED or hospital admission or more than 48 hours after hospital discharge. Patients with these criteria were excluded to prevent bias in either direction.

Patients were grouped by the presence of alcohol withdrawal, septic shock, TBI, or DKA alone; alcohol withdrawal in combination with each of the other diagnoses; or alcohol withdrawal with more than 1 other diagnosis (8 categories total) (**Figure**; **Appendix Table 1**, available at Annals.org).

Statistical Analysis

Descriptive statistics were used to characterize the study sample. Continuous data were reported as means with SDs or medians with interquartile ranges, based on the distribution of the data, and categorical data were reported as counts with percentages.

The outcome of the study was the incidence of thiamine supplementation in various illness categories. The predicted probabilities of thiamine supplementation in each group, along with 95% CIs, were calculated using generalized estimating equations, specified with the binomial family of distributions and the logit link function. An exchangeable covariance structure was used to account for clustering of patients within hospitals. The model controlled for age, sex, race, comorbid conditions, year, number of beds in the hospital, whether the hospital was a teaching or nonteaching

Table 1. Demographic and Hospital-Level Factors for Patients With AUD and Exclusive* Critical Illness

Demographic/Hospital Factor	Total (*n* = 14 998 [100%])†	Alcohol Withdrawal (*n* = 10 248 [68%])	Septic Shock (*n* = 1920 [13%])	TBI (*n* = 539 [4%])	DKA (*n* = 809 [5%])
Mean age (SD), *y*	52 (13)	51 (12)	58 (12)	54 (15)	47 (13)
Male sex, *n (%)*	11 590 (77)	8044 (79)	1323 (69)	417 (78)	629 (78)
Race, *n (%)*					
White	11 020 (74)	7723 (75)	1328 (69)	404 (75)	481 (60)
African American	1762 (12)	1137 (11)	245 (13)	59 (11)	160 (20)
Other	1708 (11)	1094 (11)	247 (13)	54 (10)	130 (16)
Medical history, *n (%)*					
Congestive heart failure	1872 (13)	1066 (10)	479 (25)	34 (6)	50 (6)
Liver disease	6298 (42)	3894 (38)	1388 (72)	149 (28)	231 (29)
Diabetes	3136 (21)	1232 (12)	462 (24)	71 (13)	809 (100)
Chronic pulmonary disease	3030 (20)	1996 (20)	546 (28)	84 (16)	75 (9)
Lymphoma	49 (<1)	22 (<1)	17 (1)	3 (1)	3 (<1)
Renal disease	1169 (8)	483 (5)	434 (23)	22 (4)	74 (9)
Metastatic disease	96 (1)	48 (1)	37 (2)	2 (<1)	1 (<1)
Type of hospital, *n (%)*					
Nonteaching	5402 (36)	3827 (37)	700 (37)	88 (16)	327 (40)
Teaching	9161 (61)	6123 (60)	1154 (60)	447 (83)	458 (57)
Rural/urban status, *n (%)*					
Rural	3004 (20)	1946 (19)	424 (22)	133 (25)	157 (19)
Urban	11 994 (80)	8302 (81)	1496 (78)	406 (75)	652 (81)
Hospital beds, *n (%)*					
<5	577 (4)	394 (4)	64 (3)	12 (2)	25 (3)
6–99	1431 (10)	1177 (12)	83 (4)	8 (2)	82 (10)
100–199	2832 (19)	2036 (20)	352 (18)	47 (9)	165 (20)
200–299	2857 (19)	2028 (20)	379 (20)	50 (9)	177 (22)
300–499	3619 (24)	2387 (23)	426 (22)	239 (44)	175 (22)
≥500	3682 (25)	2226 (22)	616 (32)	183 (34)	185 (23)
Geographic location, *n (%)*					
Northeast	3868 (26)	2920 (29)	329 (17)	157 (29)	113 (14)
South	4223 (28)	2800 (27)	618 (32)	144 (27)	262 (32)
Midwest	1905 (13)	1373 (13)	166 (9)	101 (19)	113 (14)
West	5002 (33)	3155 (31)	807 (42)	137 (25)	321 (40)

AUD = alcohol use disorder; DKA = diabetic ketoacidosis; TBI = traumatic brain injury.
* Refers to 4 mutually exclusive conditions (alcohol withdrawal, septic shock, TBI, and DKA) presented in this table, totaling 13 516 patients. The remaining 1482 patients (not shown in this table but presented in Appendix Table 2, available at Annals.org) have combinations of disease conditions (e.g., alcohol withdrawal and septic shock, alcohol withdrawal and DKA).
† Refers to the full cohort of 13 516 + 1482 = 14 998 patients.

hospital, rural or urban status, and geographic census region. Mortality was stratified by illness group and thiamine supplementation status.

We described the timing of thiamine administration in each illness group by classifying the interval between time of ED admission and time of thiamine supplementation into 12-hour intervals and determining the counts and percentages of patients in each interval and illness group. Furthermore, we classified the route of thiamine administration into the following 4 categories: intravenous, intramuscular, enteral, and unknown.

All analyses were done using Stata, version 15.1 (StataCorp), and all graphics were generated using the ggplot2 package from the R statistical environment (R Foundation).

Role of the Funding Source

The study was funded by the National Institutes of Health, which had had no influence on the study's design, conduct, or reporting.

Results

Study Cohort Characteristics

Over the 8-year study period, 14 998 patients from 133 hospitals met the inclusion criteria (Figure). The mean age was 52.2 years, and 77% of participants were male. Most of the patients (78% [11 730 of 14 998]) were identified as having alcohol withdrawal, and 68% (*n* = 10 248) had alcohol withdrawal without any other illness of interest. Table 1 and Appendix Table 1 describe patient characteristics in detail.

Incidence of Thiamine Supplementation

Of the total cohort, 7689 patients (51%) received thiamine. The proportions of patients receiving thiamine for a single included illness were 59% (*n* = 6038) for alcohol withdrawal, 26% (*n* = 491) for septic shock, 41% (*n* = 220) for TBI, and 24% (*n* = 195) for DKA. After multivariate adjustment, the predicted probabilities of thiamine supplementation

Table 2. Outcomes in Patients With AUD and Exclusive Critical Illness

Subgroup of Patients With AUD	Observed Thiamine Supplementation (95% CI), %	Predicted Thiamine Supplementation (95% CI), %	Observed Mortality (95% CI), %
All*	51.3 (50.5–52.1)	47.4 (42.1–52.6)	9.3 (8.8–9.8)
Alcohol withdrawal (*n* = 10 248)	58.9 (58.0–59.9)	53.3 (47.4–59.2)	2.8 (2.5–3.1)
Septic shock (*n* = 1920)	25.6 (23.7–27.6)	25.6 (21.0–30.1)	42.3 (40.1–44.5)
TBI (*n* = 539)	40.8 (36.6–45.1)	30.3 (23.4–37.2)	9.1 (6.8–11.8)
DKA (*n* = 809)	24.1 (21.2–27.2)	27.2 (21.5–32.9)	2.3 (1.4–3.6)

AUD = alcohol use disorder; DKA = diabetic ketoacidosis; TBI = traumatic brain injury.
* Refers to the entire cohort of 14 998 patients.

were 53% (95% CI, 47% to 59%) for alcohol withdrawal, 26% (CI, 21% to 30%) for septic shock, 30% (CI, 23% to 37%) for TBI, and 27% (CI, 22% to 33%) for DKA (**Table 2**). The observed incidence and predicted probability, respectively, of thiamine supplementation in patients with AUD, alcohol withdrawal, and another critical illness were 50% and 49% (CI, 43% to 55%) for septic shock, 53% and 48% (CI, 40% to 56%) for TBI, and 55% and 58% (CI, 50% to 66%) for DKA (**Appendix Table 2**, available at Annals.org).

Thiamine was administered within 12 hours of ED presentation in 52% (*n* = 3957) of patients who received thiamine. **Table 3** and **Appendix Table 3** (available at Annals.org) describe thiamine supplementation timing in detail. The most common route of thiamine supplementation was enteral (41% [*n* = 3119]). **Table 4** describes the routes of thiamine supplementation.

Mortality

Overall mortality in the cohort was 9% (*n* = 1395). Mortality was 3% (*n* = 283) in those with alcohol withdrawal only, 42% (*n* = 812) in those with septic shock only, 9% (*n* = 49) in those with TBI only, and 2% (*n* = 19) in those with DKA only (**Table 2**). **Appendix Table 2** shows mortality data for patients with AUD and more than 1 critical illness. The total mortality in patients receiving thiamine was 6% (*n* = 456), compared with 13% (*n* = 939) in those not receiving thiamine. **Appendix Table 4** (available at Annals.org) shows mortality in each illness group stratified by thiamine supplementation status.

DISCUSSION

In this study of a large cohort of critically ill patients with AUD in the United States, approximately half of the patients admitted to the ICU with AUD did not receive thiamine. Patients with AUD who were admitted for septic shock, TBI, or DKA but lacked a diagnosis of alcohol withdrawal had both a numerically lower incidence and a lower predicted probability of receiving thiamine than those who were admitted with alcohol withdrawal.

Alcohol use is a well-recognized and important risk factor for thiamine deficiency. Alcohol use disorder is associated with reduction in dietary intake of thiamine and also inhibits intestinal absorption of thiamine, both of which lead to thiamine deficiency (3, 20). If this thiamine deficiency is left uncorrected, it may contribute to significant morbidity and mortality (1–4). Various guidelines have recognized the importance of prophylactic use of thiamine in preventing Wernicke encephalopathy (2, 5, 6, 14). The European Federation of Neurological Societies recommended prophylactic parenteral administration of thiamine in all patients at high risk for thiamine deficiency managed in the ED (5). The American Society of Addiction Medicine in their alcohol withdrawal management guidelines recommended provision of thiamine for hospitalized patients who are admitted for alcohol withdrawal or develop alcohol withdrawal during their hospital course to prevent Wernicke encephalopathy (14). Although optimal thiamine administration timing is not established, recommendations are to administer thiamine as soon as possible (6) and preferably intravenously (5) to prevent irreversible brain injury. In addition, thiamine deficiency is seen in septic shock, TBI, and DKA (3, 6, 7, 9–13), and thiamine deficiency in these illnesses in patients with underlying AUD might be more pronounced because of increased metabolic need in these conditions. Cancer, prior bariatric surgery, malabsorption due to gastrointestinal disease, parenteral

Table 3. Timing of First Thiamine Dose in Patients With AUD and Exclusive Critical Illness

Timing of Thiamine Administration	All, *n* (%)*	Alcohol Withdrawal, *n* (%)	Septic Shock, *n* (%)	Traumatic Brain Injury, *n* (%)	Diabetic Ketoacidosis, *n* (%)
≤12 h	3957 (51.5)	3258 (54.0)	196 (39.9)	87 (39.6)	86 (44.1)
12–≤24 h†	1449 (18.9)	1098 (18.2)	113 (23.0)	56 (25.5)	44 (22.6)
24–≤36 h†	505 (6.6)	389 (6.4)	26 (5.3)	21 (9.6)	18 (9.2)
36–≤48 h†	436 (5.7)	317 (5.3)	40 (8.2)	15 (6.8)	14 (7.2)
48–≤54 h†	113 (1.5)	82 (1.4)	5 (1.0)	5 (2.3)	7 (3.6)
>54 h	1229 (16.0)	894 (14.8)	111 (22.6)	36 (16.4)	26 (13.3)
Total	7689 (100.0)	6038 (100.0)	491 (100.0)	220 (100.0)	195 (100.0)

AUD = alcohol use disorder; DKA = diabetic ketoacidosis; TBI = traumatic brain injury.
* Represents the entire cohort of 14 998 patients—i.e., patients from the 4 exclusive critical illness groups and also patients with >1 critical illness group who received thiamine.
† Does not include the lower boundary of the hour grouping.

Table 4. Route of First Dose of Thiamine Administered in Patients With AUD

Route	Count, *n* (%)*
Intravenous	3075 (40.0)
Intramuscular	443 (5.8)
Enteral†	3119 (40.6)
Unknown	1052 (13.7)
Total	7689 (100.0)

AUD = alcohol use disorder.
* Represents unique patients in the data set because only the route of the first dose of thiamine for each patient is enumerated.
† Includes administration by mouth, nasogastric tube, orogastric tube, jejunostomy tube, or gastrostomy tube.

nutrition, starvation, and malnutrition are also risk factors for thiamine deficiency, although these patient populations were not the focus of the present study (5). Additional concerns in critically ill patients with thiamine deficiency (although not the focus of guidelines) include cardiovascular and gastrointestinal beriberi, which has a presentation similar to those of other underlying critically ill states, such as sepsis, and will result in death if unrecognized (21–25).

Limited single-center studies have explored thiamine supplementation in critically ill patients with AUD and have shown varying prevalence (9, 15, 26). In a single Scottish center, thiamine supplementation was seen in 21% of patients with AUD admitted to the neurosurgical unit with TBI (9). Conversely, 82% of a cohort with AUD from a single center in the United States in whom addiction psychiatry services were involved received thiamine. Our previous work on the practice pattern (26) of thiamine administration in patients with AUD and septic shock showed a thiamine supplementation incidence of 64% (15). That study found a significant mortality benefit with thiamine treatment in patients with AUD presenting with septic shock (mortality, 44% in treated vs. 79% in untreated patients; $P = 0.02$). It also uncovered a potential missed opportunity to administer thiamine in these patients in the ED, where only 15% received their first dose. We speculated that septic shock shifted the clinician's focus away from AUD, explaining to a certain degree the lower-than-expected incidence of thiamine supplementation. The study, however, was done in a single center and had a small sample size, limiting generalizability. The hypothesis proposed in that study laid the foundation for our current study in a nationwide cohort.

In our current study, just 59% of patients with AUD diagnosed only with alcohol withdrawal received thiamine supplementation. Because the alcohol-related nature of their illness was obvious, this group was most expected to receive thiamine (14). Of the patients with AUD diagnosed only with septic shock, TBI, or DKA, 26%, 41%, or 24%, respectively, received thiamine, and the adjusted predicted probabilities were similarly low. The finding that patients with AUD without overt alcohol withdrawal are numerically less likely to receive thiamine supports our earlier hypothesis that, in the face of other acute critical illnesses, clinicians may be more focused on those illnesses than AUD, which can lead to thiamine supplementation not being provided. This hypothesis is further supported by the higher incidence of thiamine supplementation in patients with septic shock, TBI, or DKA if they were also diagnosed with alcohol withdrawal. Of the patients with AUD who received thiamine, only 40% received it via the recommended intravenous route (5) and only 52% received the first dose within 12 hours of presentation. This suggests that even in patients who receive thiamine, there may be room for improvement in route and timing of administration (6).

In the early 20th century, dietary deficiency was identified as a cause of beriberi and WKS, and by the mid-20th century, thiamine specifically was identified and started being used in treatment of these diseases (4, 5, 27). Guidelines on thiamine supplementation to treat patients with AUD and alcohol withdrawal were subsequently implemented (2, 5, 6, 14). With the knowledge of the importance of prophylactic use of thiamine in AUD, one could expect a high incidence of thiamine supplementation in the 21st century. However, our study highlights a serious quality assurance issue in AUD with critical illnesses in the United States. Measures that could help improve use of thiamine supplementation include automatic flags and suggestions to administer thiamine in the electronic health record with an AUD diagnosis code, an option of thiamine administration in ED or ICU order sets while patients with AUD are being admitted, and pharmacy flags for patients with AUD (28, 29).

Our study has some limitations. First, AUD can be misclassified using ICD-9 and ICD-10 codes, leading to overestimation of thiamine underuse in AUD. However, such codes have been shown to have high positive predictive value to identify AUD (15, 18, 19), mitigating this bias. Second, specific dosing and duration of thiamine supplementation were beyond the scope of the study and were not completely captured in the database. However, we included patients who received even a single dose of thiamine by either an intravenous or an enteral route, and we anticipate that the true number of patients receiving the recommended high dose of intravenous thiamine (5, 6, 14) is lower than our reported numbers. Finally, the large sample size and the multicenter and retrospective nature of our study prevented us from verifying the data by manual review of medical records.

To conclude, in our study, approximately half of patients with AUD and critical illness did not receive thiamine supplementation. Patients with AUD admitted with septic shock, TBI, or DKA and without alcohol withdrawal were found to have numerically lower use of thiamine in their treatment than patients with alcohol withdrawal. This information highlights a potential area for quality improvement.

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Reproducible Research Statement: *Study protocol and statistical code:* Available on request (e-mail, mdonnino@bidmc.harvard.edu). *Data set:* The data cannot be shared publicly because proprietary rights belong to Cerner.

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Appendix Table 1. Demographic and Hospital-Level Factors for Patients With AUD and More Than 1* Critical Illness

Demographic/Hospital Factor	Alcohol Withdrawal and Septic Shock (*n* = 652 [4%])	Alcohol Withdrawal and TBI (*n* = 432 [3%])	Alcohol Withdrawal and DKA (*n* = 294 [1%])	Alcohol Withdrawal and ≥2 Other Illnesses (*n* = 104 [<1%])
Mean age (SD), *y*	56 (11)	54 (13)	50 (11)	54 (12)
Male sex, *n (%)*	496 (76)	356 (82)	243 (83)	82 (79)
Race, *n (%)*				
White	487 (75)	316 (73)	208 (71)	73 (70)
African American	73 (11)	52 (12)	25 (9)	11 (11)
Other	70 (11)	46 (11)	48 (16)	19 (18)
Medical history, *n (%)*				
Congestive heart failure	175 (27)	24 (6)	22 (8)	22 (21)
Liver disease	398 (62)	99 (23)	84 (29)	55 (53)
Diabetes	132 (20)	48 (11)	294 (100)	88 (85)
Chronic pulmonary disease	204 (31)	70 (16)	39 (13)	16 (16)
Lymphoma	3 (<1)	0 (0)	0 (0)	1 (1)
Renal disease	98 (15)	11 (3)	34 (12)	13 (13)
Metastatic disease	5 (1)	0 (0)	0 (0)	3 (3)
Type of hospital, *n (%)*				
Nonteaching	242 (37)	80 (19)	106 (36)	32 (31)
Teaching	384 (59)	351 (81)	179 (61)	65 (63)
Rural/urban status, *n (%)*				
Rural	140 (22)	117 (27)	65 (22)	22 (21)
Urban	512 (79)	315 (73)	229 (78)	82 (79)
Hospital beds, *n (%)*				
<5	39 (6)	24 (6)	11 (4)	8 (8)
6–99	37 (6)	7 (2)	30 (10)	7 (7)
100–199	120 (18)	32 (7)	65 (22)	15 (14)
200–299	125 (19)	34 (8)	50 (17)	14 (14)
300–499	129 (20)	175 (41)	63 (21)	25 (24)
≥500	202 (31)	160 (37)	75 (26)	35 (34)
Geographic location, *n (%)*				
Northeast	143 (22)	120 (28)	71 (24)	15 (14)
South	189 (29)	113 (26)	67 (23)	30 (29)
Midwest	60 (9)	58 (13)	29 (10)	5 (5)
West	260 (40)	141 (33)	127 (43)	54 (52)

AUD = alcohol use disorder; DKA = diabetic ketoacidosis; TBI = traumatic brain injury.
* Refers to 1482 patients who have combinations of critical illnesses (e.g., alcohol withdrawal and septic shock, alcohol withdrawal and DKA).

Appendix Table 2. Outcomes in Patients With AUD and More Than 1 Critical Illness

Subgroup of Patients With AUD	Observed Thiamine Supplementation (95% CI), %	Predicted Thiamine Supplementation (95% CI), %	Observed Mortality (95% CI), %
All*	51.3 (50.5–52.1)	47.4 (42.1–52.6)	9.3 (8.8–9.8)
Alcohol withdrawal + septic shock (*n* = 652)	49.5 (45.6–53.4)	48.8 (42.5–55.1)	27.6 (24.2–31.2)
Alcohol withdrawal + TBI (*n* = 432)	53.2 (48.4–58.0)	47.7 (39.8–55.6)	4.1 (2.4–6.5)
Alcohol withdrawal + DKA (*n* = 294)	54.8 (48.9–60.1)	58.1 (50.4–65.7)	1.7 (0.5–3.9)
Alcohol withdrawal + ≥2 other illnesses (*n* = 104)	29.8 (21.2–39.6)	34.9 (26.8–42.9)	27.9 (19.5–37.5)

AUD = alcohol use disorder; DKA = diabetic ketoacidosis; TBI = traumatic brain injury.
* Refers to the entire cohort of 14 998 patients.

Appendix Table 3. Timing of First Thiamine Dose in Patients With AUD and More Than 1 Critical Illness

Timing of Thiamine Administration	Alcohol Withdrawal + Septic Shock, *n (%)*	Alcohol Withdrawal + TBI, *n (%)*	Alcohol Withdrawal + DKA, *n (%)*	Alcohol Withdrawal + ≥2 Other Illnesses, *n (%)*
≤12 h	116 (35.9)	119 (51.7)	84 (52.2)	11 (35.5)
12–≤24 h*	67 (20.7)	38 (16.5)	29 (18.0)	4 (12.9)
24–≤36 h*	26 (8.1)	11 (4.8)	13 (8.1)	1 (3.2)
36–≤48 h*	19 (5.9)	14 (6.1)	13 (8.1)	4 (12.9)
48–≤54 h*	7 (2.2)	3 (1.3)	3 (1.9)	1 (3.2)
>54 h	88 (27.2)	45 (19.6)	19 (11.8)	10 (32.3)
Total	323 (100.0)	230 (100.0)	161 (100.0)	31 (100.0)

AUD = alcohol use disorder; DKA = diabetic ketoacidosis; TBI = traumatic brain injury.
* Does not include the lower boundary of the hour grouping.

Appendix Table 4. Mortality in Different Illnesses, by Thiamine Supplementation Status

Patients With AUD	Thiamine Receivers (*N* = 7689), *n/N (% [95% CI])*	Thiamine Nonreceivers (*N* = 7309), *n/N (% [95% CI])*
Alcohol withdrawal	135/6038 (2.2 [1.9–2.6])	148/4210 (3.5 [3.0–4.1])
Septic shock	190/491 (38.7 [34.4–43.2])	622/1429 (43.5 [40.9–46.1])
TBI	18/220 (8.2 [4.9–12.6])	31/319 (9.7 [6.7–13.5])
DKA	4/195 (2.1 [0.6–5.2])	15/614 (2.4 [1.4–4.0])
Alcohol withdrawal + septic shock	92/323 (28.5 [23.6–33.7])	88/329 (26.8 [22.0–31.9])
Alcohol withdrawal + TBI	9/230 (3.9 [1.8–7.3])	9/202 (4.5 [2.1–8.3])
Alcohol withdrawal + DKA	2/161 (1.2 [0.2–4.4])	3/133 (2.3 [0.5–6.5])
Alcohol withdrawal + ≥2 other illnesses	6/31 (19.3 [7.5–37.5])	23/73 (31.5 [21.1–43.4])
Total mortality	456/7689 (5.9 [5.4–6.5])	939/7309 (12.9 [12.1–13.6])

DKA = diabetic ketoacidosis; TBI = traumatic brain injury.