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Clinical Characteristics and Outcomes Associated with High Dose Intravenous Thiamine Administration in Patients with Encephalopathy

Zev M Nakamura, MD¹, Jason R Tatreau, MD¹, Donald L Rosenstein, MD^{1,2}, and Eliza M Park, MD^{1,2}

¹Department of Psychiatry, University of North Carolina, 101 Manning Drive, CB #7160, Chapel Hill, NC 27599, USA

²Department of Medicine, University of North Carolina, 125 MacNider Hall, CB#7005, Chapel Hill, NC 27599, USA

Abstract

Background—Wernicke’s encephalopathy (WE) is a common neuropsychiatric syndrome due to thiamine deficiency. There is no consensus regarding thiamine dosing when WE is suspected. A longstanding dosing strategy for WE is 100 mg daily, yet updated clinical guidelines suggest using high dose intravenous thiamine (HDIV).

Objective—To describe thiamine prescribing practices at a large, public academic hospital and investigate clinical characteristics and outcomes associated with HDIV thiamine in patients with encephalopathy who received IV thiamine.

Methods—Electronic medical records of hospitalized patients who received thiamine between 4/4/2014 and 11/1/2015 were reviewed. Chi-square tests, Wilcoxon Rank Sum tests, and logistic regression were used to compare clinical variables in patients with encephalopathy who received HDIV thiamine (200 mg twice daily) vs. lower doses of IV thiamine.

Results—Among the total 5,236 thiamine orders, 29% (n=1,531) were IV; 10% (n=150) of IV orders met HDIV criteria. In patients with encephalopathy who received IV thiamine (n=432), HDIV thiamine was administered to 20% (n=86) and only 2.1% (n=9) received dosing consistent with Royal College of Physicians guidelines. In bivariable analyses, HDIV thiamine was associated with surgical services (p=0.001), psychiatric consultation (p<0.001), and decreased mortality (p=0.004). In multivariable models, the association between HDIV thiamine and decreased in-hospital mortality did not meet statistical significance (p=0.061).

Corresponding author at: Zev M Nakamura, MD, Department of Psychiatry, University of North Carolina, 101 Manning Drive, Campus Box #7160, Chapel Hill, NC 27599 USA, Phone: 984-974-3829, Fax: 984-974-9646, zev.nakamura@unchealth.unc.edu.

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Conclusions—In a large, public academic hospital, guideline-concordant thiamine supplementation is rare and HDIV thiamine is infrequently prescribed to patients with encephalopathy. Further studies are needed to confirm the possible benefits of HDIV thiamine for patients with suspected thiamine-deficient encephalopathy.

Keywords

thiamine deficiency; Wernicke's encephalopathy; Wernicke-Korsakoff Syndrome

Introduction

Wernicke-Korsakoff Syndrome (WKS) represents a spectrum of neuropsychiatric presentations due to vitamin B1 (thiamine) deficiency. It includes both acute mental status changes (Wernicke's encephalopathy, WE) and can progress to an irreversible dementia with marked anterograde amnesia (Korsakoff's syndrome). Though it is most commonly associated with alcoholism, WE occurs in 2% of the general population¹ and has been described in a wide array of medical illnesses (e.g. Acquired Immunodeficiency Syndrome,² acute pancreatitis,³ inflammatory bowel disease,⁴ malignancy,⁵ and thyrotoxicosis⁶) or as a consequence of medical interventions, such as bariatric surgery⁷ and total parenteral nutrition.^{8,9}

WE is a clinical diagnosis, based on the triad of mental status changes, ophthalmoplegia, and ataxia. The single most common sign of WE is mental status changes, documented in 82%, whereas ophthalmologic and cerebellar signs occur less than 30% of the time.¹⁰ Post-mortem studies reveal that over 80% of cases of WE go undiagnosed during patients' lifetimes, which suggests that the diagnostic criteria for WE may be overly restrictive.^{11,12} The role of diagnostic studies in WE is also limited. Specifically, while there are established radiologic findings observable on Magnetic Resonance Imaging (MRI) of the brain, they are only present in about half of WE cases.¹³

Thiamine deficiency is a very common finding in the medically ill with studies reporting a prevalence of 30% in critically ill populations,¹⁴ 33% in heart failure patients,¹⁵ and in one small cohort study, 100% in bone marrow transplant recipients.¹⁶ While thiamine deficiency can support the diagnosis of WE, the utility of thiamine levels is limited in that only highly specialized laboratories are able to perform thiamine measurements, delaying their availability for timely clinical management. Also, it is not clear how thiamine levels in plasma correlate with levels in the central nervous system, where thiamine deficiency leads to the neuropsychiatric symptomatology seen in WE. Few studies have investigated co-occurring rates of thiamine deficiency and altered mental status independent of a formal WE diagnosis, but one retrospective series of hospitalized oncology patients found that thiamine deficiency occurred in 55% (n=217), 80% of whom demonstrated some altered mental status abnormality.¹⁷

There is no consensus for thiamine replacement in the treatment of WE. Intravenous (IV) and intramuscular (IM) formulations are universally preferred over the oral route since they take advantage of non-saturable simple diffusion across the blood brain barrier. By contrast, it has been shown that for oral doses exceeding 30 mg no more than 4.5 mg is absorbed

through the gut.¹⁸ Also, while not as cheap as thiamine tablets, thiamine hydrochloride for injectable use is an extremely cost-effective way to reduce morbidity and mortality in afflicted populations.

One longstanding dosing strategy for WE, described on thiamine package inserts, is 100 mg IV daily.¹⁹ This recommendation was developed over 50 years ago, has no clinical studies validating its efficacy, and is widely criticized as being inadequate.^{10,20–22} Currently, there are two sets of updated clinical guidelines for WE, one from the European Federation of Neurological Societies (EFNS) and the other from the Royal College of Physicians (RCP), both recommending higher doses of thiamine of 200 mg three times daily (TID).^{23,24} Several publications describe clinical benefit from using these higher doses of IV thiamine, but existing data are limited to case series.^{25–27}

Because WE is inaccurately believed to be rare, seen only in alcoholism, and, as a result of overly strict diagnostic criteria, frequently overlooked and mismanaged in hospitalized patients,²² it is possible that thiamine deficiency is associated with a broader spectrum of neuropsychiatric conditions. Similar concerns have been expressed previously by Isenberg-Grzeda and colleagues who proposed the term “thiamine-related encephalopathy” as an alternative to WE.^{25,26} In light of poor diagnostic sensitivity to encephalopathy related to thiamine deficiency and lacking evidence to support a specific treatment strategy for these patients, our objectives were to describe thiamine prescribing practices and investigate clinical characteristics and outcomes associated with the use of high dose IV (HDIV) thiamine for patients with encephalopathy at a large, public academic hospital.

Methods

Study Design

We performed a retrospective cohort study of adults hospitalized at a large, public academic hospital between 4/4/2014 and 11/1/2015, who received at least one dose of thiamine 50 mg via any route. A subset of individuals, who received IV thiamine and a diagnosis of altered mental status (Appendix A), were further classified as having received HDIV thiamine or low dose IV (LDIV) thiamine. We defined HDIV thiamine as 200 mg twice daily (BID) for two doses for two reasons: (1) this is higher dosing than what is prescribed as a part of any automatic electronic order set at our institution, indicating intentionality on the part of prescribing physicians to exceed standard dosing; and (2) current high dose guidelines recommend 200 mg per dose. LDIV thiamine was defined as any prescription for IV thiamine that did not meet HDIV criteria. Only data from index hospitalizations during this time period were analyzed. This study was approved by the University of North Carolina Chapel Hill Institutional Review Board.

Data Collection

Data were extracted from a medical records data warehouse using Business Objects™ software (SAP America; Newton Square, PA). We extracted data regarding thiamine dose, frequency, and route of administration, as well as the following clinical characteristics: hospital service, age, gender, orders for one-to-one observation and restraints, psychiatric

consultation, and concomitant benzodiazepine and antipsychotic prescriptions. Benzodiazepine doses were converted to lorazepam equivalents using the method described by Jaegar et al.²⁸ All antipsychotic doses received were converted to haloperidol equivalents using the method described by Andreasen et al.²⁹ The primary clinical outcomes of interest were in-hospital mortality and length of stay.

Data Analysis

We used descriptive statistics (frequency distributions, means, ranges, and standard deviations as appropriate) to characterize the total sample and the HDIV and LDIV thiamine groups separately. To evaluate associations between receipt of HDIV vs. LDIV thiamine in patients with encephalopathy with outcomes and characteristics of interest, we compared the percentage, medians, and means of patients in each group who developed the outcomes of interest using a Chi-squared test or Fisher's Exact test for categorical outcomes and t-tests and Wilcoxon Rank Sum tests for continuous outcomes. A formal power analysis was not performed; the entire available population was included. The associations between HDIV and in-hospital mortality were examined by logistic regression models that adjusted for variables associated with in-hospital mortality at the 0.10 significance level in bivariate analyses or were commonly associated with in-hospital mortality in the literature.^{30–33} All statistical tests were two-tailed and all analyses were performed using STATA version 14 (StataCorp LP; College Station, TX).

Results

Thiamine prescribing practices

During the study period, 5,236 thiamine orders were prescribed. Oral thiamine represented over 70% (n=3,691), IV 29% (n=1,531), and IM < 0.3% (n=14) of thiamine prescriptions. Seventy nine percent (n=4,143) of all prescriptions were for once daily doses. Among IV prescriptions, approximately 30% (n=430) of IV prescriptions reflected what is listed on the package insert for WE (100 mg IV daily), and only 10% (n=150) met the HDIV standard established for this study (Table 1). Among patients with encephalopathy who were prescribed IV thiamine (n=432), only 20% (n=86) received HDIV thiamine and only 2.1% (n=9) received 500 mg IV TID, as recommended by the RCP (Table 2).

Comparison of thiamine dosing strategies for patients with encephalopathy by hospital service

The majority of IV thiamine prescriptions were ordered by medicine, medicine subspecialty, and surgery services. Surgery services were more likely to prescribe HDIV thiamine compared to non-surgical services (29% vs. 20%, $p=0.001$). LDIV thiamine was more common in the intensive care unit (ICU) compared to other services (96% vs. 80%, $p=0.034$), and otherwise there were no differences in the prescription of HDIV vs. LDIV among hospital services in patients with encephalopathy (Table 2).

Clinical characteristics in patients with encephalopathy who were prescribed IV thiamine

The likelihood of psychiatric consultation was three times higher in the HDIV than LDIV group (76% vs. 25%, $p<0.001$). Further review of the medical records for the 65 patients in

the HDIV group who received psychiatry consultation revealed that in 69% (n=45) the higher thiamine dosing was directly the result of recommendations from the consultation-liaison (CL) psychiatrists. There was no association between IV thiamine dosage and restraints, one-to-one observation, or receipt of antipsychotic and benzodiazepine medications (Table 3).

Clinical outcomes in patients with encephalopathy who were prescribed IV thiamine

In-hospital mortality was observed in 11% (n=48) of patients diagnosed with altered mental status and who received IV thiamine. In bivariate analyses, lower mortality was observed in the HDIV thiamine group compared to the LDIV thiamine group (2% vs. 13%, $p=0.004$) (Table 3). After adjusting for other factors associated with in-hospital mortality from the literature (age, male gender, length of stay) and from our own data (restraints and medicine, surgery, and ICU services), the association between receipt of HDIV thiamine and decreased odds of mortality approached, but did not reach, significance ($p=0.061$). There were no statistically significant differences between groups for hospital length of stay. Additional analyses focused on the nine subjects with encephalopathy who received the highest standard of high dose treatment (500 mg IV TID) as defined by the RCP. When this cohort was compared to patients receiving lower dose IV thiamine, no statistically significant differences between groups were found.

Discussion

Our study revealed that in a large, public academic hospital, patients with encephalopathy, who were prescribed IV thiamine, received treatment in line with high dose guidelines from the RCP only 2.1% of the time, despite greater efficacy of high dose treatment described in the literature^{23–27,34} and our finding that HDIV thiamine was associated with decreased mortality in bivariable analyses. HDIV thiamine prescription in patients with encephalopathy occurred more often on surgical services and with psychiatric consultation. Our findings highlight a delay in providers to change longstanding practices for treatment of WE to reflect more recent guidelines and the benefit of psychiatric consultation in the complex management of patients with encephalopathy.

The only other hospital-wide study of thiamine prescribing practices comes from a Canadian health care system in which 57.6% of all thiamine prescriptions were administered IV.³⁵ Virtually all thiamine (92.7%) was dosed at 100 mg and 74.6% of prescriptions were given once daily. Compared to what was reported in Day et al.'s study, IV thiamine was prescribed approximately half as often at our institution (29%) and the strength of the dose prescribed was far more variable. The distribution of dose frequency was similar with 79% of prescriptions at our institution being once daily. Both the existing literature and our findings highlight the preference of prescribers for oral over IV or IM thiamine. In our study, even those diagnosed with encephalopathy and prescribed IV thiamine rarely received HDIV thiamine. While there are multiple potential explanations for this, we suspect that one contributing factor is that for decades 100 mg IV daily has been the accepted recommendation for treatment of WE. Further, though recent developments have questioned the efficacy of the 100 mg IV daily dose, it remains on the package insert. Finally, while

more current EFNS and RCP guidelines recommend higher doses, the evidence base for these guidelines remains limited to one double-blind randomized controlled trial comparing effects of IM thiamine ranging from 5–200 mg daily,³⁴ estimations drawn from the pharmacokinetics of thiamine,²⁰ unpublished trials, and clinical experience of a select group of experts.^{21,23,24}

To our knowledge, this is the first study to investigate head-to-head differences in clinical variables in the setting of treatment with HDIV thiamine compared to lower dose strategies. Perhaps the most interesting outcome in our study was the bivariate association between HDIV thiamine with lower in-hospital mortality. After controlling for several potential confounders, the association between HDIV and lower mortality did not meet statistical significance ($p=0.061$), but may suggest additional clinical benefits with high dose IV thiamine warranting further investigation in larger and prospective samples, particularly given that mortality was a rare event in our sample.

It is not completely surprising that HDIV use was more common in surgical services given that there is a parallel body of literature in surgical and critical care settings linking thiamine deficiency to inadequate tissue perfusion and lactic acidosis that has attracted attention to thiamine status and adequate supplementation in certain high risk populations.^{14,36–38} Interestingly, we found that LDIV was actually more often prescribed in ICU settings compared to non-ICU services. This may reflect differences in the surgical vs. ICU departments at our institution regarding awareness of this body of literature or their interpretation of these findings.

HDIV prescription to patients with encephalopathy was much more common in the setting of psychiatric consultation. Of note, the higher thiamine dosing was the result of the recommendation of the psychiatric consultant in close to 70% of these cases. This could suggest an enhanced familiarity of evidence based treatments for delirium due to thiamine deficiency among CL psychiatrists. Alternatively, it may reflect the propensity for psychiatric consultation to occur in more medically and behaviorally complicated patients after more routine interventions have failed. Despite familiarity with high dose thiamine treatment in suspected thiamine-related encephalopathy among psychiatric consultants, IV thiamine was only administered once on inpatient psychiatric units to the cohort observed in our study. This is not surprising, as delirium is typically managed in medical settings rather than inpatient psychiatric settings. Further, IV lines are atypically utilized on the inpatient psychiatric units at our institution due to safety concerns.

Limitations

There are several limitations of our study. First, because it was retrospective, we were unable to make determinations regarding causality. Related to this, we were unable to perform in-depth chart review on the subjects included in the study, so the rationale for thiamine prescription in each case was not known, and study outcomes were constrained by those that could be easily extracted. Despite our large sample size, our study was not powered to detect differences between groups that received guideline-concordant HDIV vs. lower thiamine doses due to the small number of patients who received guideline-concordant doses of IV thiamine during the study period. As a result, we defined HDIV at a lower threshold of 200

mg BID. Though we believe that our results still elucidate the potential efficacy of high dose IV strategies, we were unable to specifically comment on the efficacy of high dose IV guidelines from the EFNS or RCP.

Conclusions

WE is described in 2% of the general population,³⁹ but in our cohort of patients with altered mental status determined to require IV thiamine, where one would suspect a much higher prevalence of WE, <1% (n=4) formally received WE or WKS diagnoses. This discrepancy highlights the limited utility of continuing to use the eponymous term to describe this condition and supports a transition to a more accurate and management-relevant diagnosis. We propose the term thiamine-deficient encephalopathy (TDE) as a more descriptive and inclusive name, which may potentially facilitate awareness of altered mental status resulting from or exacerbated by thiamine deficiency and guide appropriate treatment. This redefining of WE as TDE is supported by criteria developed by Caine and colleagues, in which the diagnosis requires only two of the following: (1) signs of malnutrition, (2) mild memory impairment or confusion, (3) eye signs, and (4) cerebellar signs. In Caine's criteria, *signs of malnutrition* is an inclusive criterion, including abnormal thiamine status, BMI two standard deviations below normal, or grossly impaired dietary intake. Caine's criteria has an impressive 94% sensitivity and 99% specificity for diagnosis of WE and related syndromes.⁴⁰

The widespread use of TDE would provide a meaningful step towards better identification of patients afflicted with the neuropsychiatric manifestations of thiamine deficiency. It is at least as important that clinicians work to familiarize themselves with the wide array of medical conditions in which thiamine deficiency occurs and increase their awareness to the potential for thiamine deficiency to lead to acute changes in mental status. More widespread use of the Caine criteria may lead to gains in this direction. More readily available and diagnostically reliable assays would also likely be necessary for increased sensitivity to the diagnosis. There is an equally critical need for consensus regarding appropriate treatment of TDE when it is diagnosed. In order to arrive at a treatment consensus, prospective studies in high risk populations evaluating the efficacy of high dose IV thiamine are needed.

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References

1. Lishman WA. Cerebral disorder in alcoholism: syndromes of impairment. *Brain*. 1981 Mar; 104(Pt 1):1–20. [PubMed: 7470838]
2. Boldorini R, Vago L, Lechi A, Tedeschi F, Trabattoni GR. Wernicke's encephalopathy: occurrence and pathological aspects in a series of 400 AIDS patients. *Acta Biomed Ateneo Parmense*. 1992; 63(1–2):43–9. [PubMed: 1340667]

3. Sun GH, Yang YS, Liu QS, Cheng LF, Huang XS. Pancreatic encephalopathy and Wernicke encephalopathy in association with acute pancreatitis: a clinical study. *World J Gastroenterol*. 2006 Jul 14; 12(26):4224–7. [PubMed: 16830380]
4. Larnaout A, El-Euch G, Kchir N, Filali A, Hamida MB, Hentati F. Wernicke's encephalopathy in a patient with Crohn's disease: a pathological study. *J Neurol*. 2001 Jan; 248(1):57–60. [PubMed: 11266021]
5. Kuo SH, Debnam JM, Fuller GN, de Groot J. Wernicke's encephalopathy: an underrecognized and reversible cause of confusional state in cancer patients. *Oncology*. 2009; 76(1):10–8. [PubMed: 19018150]
6. Bonucchi J, Hassan I, Policeni B, Kaboli P. Thyrotoxicosis associated Wernicke's encephalopathy. *J Gen Intern Med*. 2008 Jan; 23(1):106–9. [PubMed: 18026802]
7. Aasheim ET. Wernicke encephalopathy after bariatric surgery: a systematic review. *Ann Surg*. 2008 Nov; 248(5):714–20. [PubMed: 18948797]
8. Hahn JS, Berquist W, Alcorn DM, Chamberlain L, Bass D. Wernicke encephalopathy and beriberi during total parenteral nutrition attributable to multivitamin infusion shortage. *Pediatrics*. 1998 Jan; 101(1):E10.
9. Nakasaki H, Ohta M, Soeda J, Makuuchi H, Tsuda M, Tajima T, et al. Clinical and biochemical aspects of thiamine treatment for metabolic acidosis during total parenteral nutrition. *Nutrition*. 1997 Feb; 13(2):110–7. [PubMed: 9106788]
10. Harper CG, Giles M, Finlay-Jones R. Clinical signs in the Wernicke-Korsakoff complex: a retrospective analysis of 131 cases diagnosed at necropsy. *J Neurol Neurosurg Psychiatry*. 1986 Apr; 49(4):341–5. [PubMed: 3701343]
11. Harper C. The incidence of Wernicke's encephalopathy in Australia--a neuropathological study of 131 cases. *J Neurol Neurosurg Psychiatry*. 1983 Jul; 46(7):593–8. [PubMed: 6886695]
12. Harper C. Wernicke's encephalopathy: a more common disease than realised. A neuropathological study of 51 cases. *J Neurol Neurosurg Psychiatry*. 1979 Mar; 42(3):226–31. [PubMed: 438830]
13. Antunez E, Estruch R, Cardenal C, Nicolas JM, Fernandez-Sola J, Urbano-Marquez A. Usefulness of CT and MR imaging in the diagnosis of acute Wernicke's encephalopathy. *AJRAmerican J Roentgenol*. 1998 Oct; 171(4):1131–7.
14. Donnino MW, Carney E, Cocchi MN, Barbash I, Chase M, Joyce N, et al. Thiamine deficiency in critically ill patients with sepsis. *J Crit Care*. 2010 Dec; 25(4):576–81. [PubMed: 20646908]
15. Schoenenberger AW, Schoenenberger-Berzins R, der Maur CA, Suter PM, Vergopoulos A, Erne P. Thiamine supplementation in symptomatic chronic heart failure: a randomized, double-blind, placebo-controlled, cross-over pilot study. *Clin Res Cardiol*. 2012 Mar; 101(3):159–64. [PubMed: 22057652]
16. Nannya Y, Shinohara A, Ichikawa M, Kurokawa M. Serial profile of vitamins and trace elements during the acute phase of allogeneic stem cell transplantation. *Biol Blood Marrow Transplant*. 2014 Mar; 20(3):430–4. [PubMed: 24333749]
17. Isenberg-Grzeda E, Shen MJ, Alici Y, Wills J, Nelson C, Breitbart W. High rate of thiamine deficiency among inpatients with cancer referred for psychiatric consultation: results of a single site prevalence study. *Psychooncology*. 2016 May 26.
18. Thomson AD. Mechanisms of vitamin deficiency in chronic alcohol misusers and the development of the Wernicke-Korsakoff syndrome. *Alcohol Alcohol (Oxford, Oxfordshire)Supplement*. 2000; 35(1):2–7.
19. APP Pharmaceuticals LLC. Thiamine Hydrochloride Injection, USP [Internet]. Schaumburg, Illinois: APP Pharmaceuticals, LLC; 2008. Available from: http://editor.fresenius-kabi.us/PIS/Thiamine_Inj_45819E_May_08.pdf
20. Donnino MW, Vega J, Miller J, Walsh M. Myths and misconceptions of Wernicke's encephalopathy: what every emergency physician should know. *Ann Emerg Med*. 2007 Dec; 50(6):715–21. [PubMed: 17681641]
21. Cook CC, Hallwood PM, Thomson AD. B Vitamin deficiency and neuropsychiatric syndromes in alcohol misuse. *Alcohol Alcohol*. 1998; 33(4):317–36. [PubMed: 9719389]
22. Isenberg-Grzeda E, Kutner HE, Nicolson SE. Wernicke-Korsakoff-syndrome: under-recognized and under-treated. *Psychosomatics*. 2012; 53(6):507–16. [PubMed: 23157990]

23. Galvin R, Brathen G, Ivashynka A, Hillbom M, Tanasescu R, Leone MA, et al. EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy. *Eur J Neurol*. 2010 Dec; 17(12):1408–18. [PubMed: 20642790]
24. Thomson AD, Cook CC, Touquet R, Henry JA. Royal College of Physicians L. The Royal College of Physicians report on alcohol: guidelines for managing Wernicke's encephalopathy in the accident and Emergency Department. *Alcohol Alcohol*. 2002; 37(6):513–21. [PubMed: 12414541]
25. Isenberg-Grzeda E, Alici Y, Hatzoglou V, Nelson C, Breitbart W. Nonalcoholic Thiamine-Related Encephalopathy (Wernicke-Korsakoff Syndrome) Among Inpatients With Cancer: A Series of 18 Cases. *Psychosomatics*. 2016; 57(1):71–81. [PubMed: 26791514]
26. Isenberg-Grzeda E, Hsu AJ, Hatzoglou V, Nelso C, Breitbart W. Palliative treatment of thiamine-related encephalopathy (Wernicke's encephalopathy) in cancer: A case series and review of the literature. *Palliat Support Care*. 2015 Oct; 13(5):1241–9. [PubMed: 25339378]
27. Nishimoto A, Usery J, Winton JC, Twilla J. High-dose Parenteral Thiamine in Treatment of Wernicke's Encephalopathy: Case Series and Review of the Literature. *In Vivo*. 2017 Jan 2; 31(1): 121–4. [PubMed: 28064230]
28. Jaeger TM, Lohr RH, Pankratz VS. Symptom-triggered therapy for alcohol withdrawal syndrome in medical inpatients. *Mayo Clin Proc*. 2001 Jul; 76(7):695–701. [PubMed: 11444401]
29. Andreasen NC, Pressler M, Nopoulos P, Miller D, Ho BC. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. *Biol Psychiatry*. 2010 Feb 1; 67(3):255–62. [PubMed: 19897178]
30. Van Den Noortgate N, Vogelaers D, Afschrift M, Colardyn F. Intensive care for very elderly patients: outcome and risk factors for in-hospital mortality. *Age Ageing*. 1999 May; 28(3):253–6. [PubMed: 10475859]
31. Silva TJA, Jerussalmy CS, Farfel JM, Curiati JAE, Jacob-Filho W. Predictors of in-hospital mortality among older patients. *Clinics (Sao Paulo)*. 2009; 64(7):613–8. [PubMed: 19606235]
32. Thomas JM, Cooney LMJ, Fried TR. Systematic review: Health-related characteristics of elderly hospitalized adults and nursing home residents associated with short-term mortality. *J Am Geriatr Soc*. 2013 Jun; 61(6):902–11. [PubMed: 23692412]
33. Asadollahi K, Hastings IM, Beeching NJ, Gill GV. Laboratory risk factors for hospital mortality in acutely admitted patients. *QJM*. 2007 Aug; 100(8):501–7. [PubMed: 17609227]
34. Ambrose ML, Bowden SC, Whelan G. Thiamin treatment and working memory function of alcohol-dependent people: preliminary findings. *Alcohol Clin Exp Res*. 2001 Jan; 25(1):112–6. [PubMed: 11198705]
35. Day GS, Ladak S, Curley K, Farb NA, Masiowski P, Pringsheim T, et al. Thiamine prescribing practices within university-affiliated hospitals: a multicenter retrospective review. *J Hosp Med*. 2015 Apr; 10(4):246–53. [PubMed: 25652810]
36. Moskowitz A, Graver A, Giberson T, Berg K, Liu X, Uber A, et al. The relationship between lactate and thiamine levels in patients with diabetic ketoacidosis. *J Crit Care*. 2014 Feb; 29(1): 182.e5–182.e8.
37. Manzanares W, Hardy G. Thiamine supplementation in the critically ill. *Curr Opin Clin Nutr Metab Care*. 2011 Nov; 14(6):610–7. [PubMed: 21912244]
38. Falder S, Silla R, Phillips M, Rea S, Gurfinkel R, Baur E, et al. Thiamine supplementation increases serum thiamine and reduces pyruvate and lactate levels in burn patients. *Burns*. 2010 Mar; 36(2):261–9. [PubMed: 19501976]
39. Torvik A. Wernicke's encephalopathy--prevalence and clinical spectrum. *Alcohol Alcohol (Oxford, Oxfordshire)Supplement*. 1991; 1:381–4.
40. Caine D, Halliday GM, Kril JJ, Harper CG. Operational criteria for the classification of chronic alcoholics: identification of Wernicke's encephalopathy. *J Neurol Neurosurg Psychiatry*. 1997 Jan; 62(1):51–60. [PubMed: 9010400]

Table 1

Thiamine Prescribing Practices

Route	Frequency	Thiamine dose (mg)				N (%)
		<100	100–175	200–275	300–500	
PO *	Once	4	133	8	26	171 (3.3)
	Daily **	280	2502	604	16	3402 (64.9)
	BID ^	5	1	84	4	94 (1.8)
	TID/QID ***	0	10	6	8	24 (<1)
IV		289 (5.5)	2646 (50.5)	702 (13.4)	54 (1.0)	3691 (70.5)
	Once	0	406	165	10	581 (11.1)
	Daily **	3	430	302	6	741 (14.1)
	BID ^	0	11	109	4	124 (2.4)
	TID/QID ***	1	47	16	21	85 (1.6)
		4 (<1)	894 (17.1)	592 (11.3)	41 (<1)	1531 (29.2)

Abbreviations: PO=oral, IV=intravenous, BID=twice daily, TID=three times daily, QID=four times daily

* PO includes NG, G-tube, J-tube, and PEG.

** Daily includes nightly and q24 hours.

^ BID includes q12 hours.

*** TID/QID includes q8 hours and q6 hours.

Note, IM orders (n=14, <0.3%) were excluded given the low frequency of this route. All thiamine orders not documented as given based on the medication administration record are excluded.

Table 2

Comparison of Demographic Characteristics in Patients with Encephalopathy based on HDIV vs. LDIV Thiamine Prescription

	Any IV	HDIV	LDIV	
	N = 432	N = 86	N = 346	P value
	N (%)	N (%)	N (%)	
Male Gender *	303 (70)	61 (71)	242 (70)	0.77
Mean Age in years, M (SD)	54 (14)	57 (13)	54 (14)	0.98
Service **				
ED	5	0 (0)	15 (100)	0.26
ICU	26	1 (4)	25 (96)	0.034
Medicine	139	28 (20)	111 (80)	0.93
Medicine Subspecialty	99	13 (13)	86 (87)	0.054
Neurology	14	2 (14)	12 (86)	0.59
Psychiatry	1	1 (100)	0 (0)	0.62
Surgery	139	41 (29)	98 (71)	0.001
OBGYN	9	1 (11)	8 (89)	0.50

Abbreviations: HDIV = high dose IV thiamine, LDIV = low dose IV thiamine, ED = emergency department, ICU = intensive care unit, OBGYN = obstetrics and gynecology, SD = standard deviation

* For Male Gender, % shown is % of Any IV, HDIV, LDIV recipients who were male

** For Service, % shown is % of IV thiamine recipients within each specified service who received HDIV vs. LDIV

Table 3

Comparison of Clinical Characteristics and Outcomes in Patients with Encephalopathy based on HDIV vs. LDIV Thiamine Prescription

	HDIV		LDIV		
Characteristic	Total sample (N = 86)		Total sample (N = 346)		
	N	Mean or %	N	Mean or %	P value
Psychiatric Consultation	65	76	87	25	<0.001
Restraints	50	58	192	55	0.66
1:1 Observer	10	12	37	11	0.80
Benzodiazepines					
Any	58	67	229	66	0.83
mg lorazepam/day		0.64		0.35	0.46
Antipsychotics					
Any	26	30	97	28	0.69
mg haloperidol/day		0		0	0.89
Length of Stay		8*		7*	0.14
Mortality	2	2	46	13	0.004

Abbreviations: HDIV = high dose IV thiamine, LDIV = low dose IV thiamine, mg = milligrams

* Median number of days