ABSTRACT

30-year-old male with family history of alcohol dependence in his father, presented to the emergency with acute pancreatitis and delirium. At age 28, he had had his first episode of acute pancreatitis and alcohol withdrawal delirium with convulsions, which was managed conservatively. Six days prior to presentation, recurrence of pancreatitis forced him to abstain from alcohol, and he developed DT and a withdrawal seizure. On examination, he was disorientated (time, place, and person), agitated, speaking irrelevantly, having visual hallucinations, and coarse tremors of hands. Serum lipase (662 units) and amylase (219 units) were raised. An ultrasound of abdomen showed a fatty liver with bulky pancreas and peripancreatic fluid. He was started on intramuscular thiamine and slow intravenous lorazepam, but did not improve and had to be intermittently physically restrained to prevent him from harming himself. Conservative management for pancreatitis was given. Over 24 hours, despite 48mg of intravenous lorazepam, he continued to have disorientation, tremors, agitation, irrelevant speech, visual hallucinations, and sleep disturbance. He was then transferred from the surgical ward to the de-addiction unit.

KEYWORDS: alcohol dependence, peripancreatic fluid, Serum lipase (662 units).
INTRODUCTION
Alcohol withdrawal symptoms range from minor tremulousness and insomnia to withdrawal seizures and DT.\cite{1,2} Symptom spectrum is similar for successive episodes of alcohol withdrawal; the range and severity of symptoms being generally proportionate to the pattern of recent alcohol intake.\cite{3}

CASE REPORT
30-year-old male with family history of alcohol dependence in his father, presented to the emergency with acute pancreatitis and delirium. Drinking alcohol and chewing tobacco since the age of 20 years, he had become dependent on these by the age of 22 and 25 years, respectively. At age 28, he had had his first episode of acute pancreatitis and alcohol withdrawal delirium with convulsions, which was managed conservatively. After an abstinence of three months he had a relapse for alcohol dependence. He had attempted multiple abstinences from alcohol, ending in severe withdrawal symptoms and seizures after 24 to 48 hours of the last intake. Scared of the seizures, he continued using 500 to 750 mL/day of 42.7 v/v spirits, without seeking medical help. About three months prior to index presentation, the stress of splitting of his joint family led to alcohol intake increasing to about 1000 mL/day, along with frequent blackouts. Six days prior to presentation, recurrence of pancreatitis forced him to abstain from alcohol, and he developed DT and a withdrawal seizure.

On examination, he was disorientated (time, place, and person), agitated, speaking irrelevantly, having visual hallucinations, and coarse tremors of hands. His laboratory parameters were normal for hemoglobin, total leucocyte count, electrolytes, urea, creatinine, bilirubin, alkaline phosphatase, total protein, albumin, but abnormal for serum glutamic oxaloacetic transaminase (SGOT)/serum glutamic pyruvic transaminase (SGPT) (90/60 units), serum calcium (8.3 units), lipase (662 units), amylase (219 units), magnesium (1.56 units), and inorganic phosphate (1.6 units).

An ultrasound of abdomen showed a fatty liver with bulky pancreas and peripancreatic fluid. Surface antigen of the hepatitis-B virus (HBsAg) and hepatitis-C virus, hepatitis-B virus, and Venereal Disease Research Laboratory screenings were all non-reactive.

He was started on intramuscular thiamine 100mg and slow intravenous lorazepam, up to 15mg/day, but did not improve and had to be intermittently physically restrained to prevent
him from harming himself. Conservative management for pancreatitis was given. For severe agitation, deep intramuscular haloperidol 5mg plus promethazine 40 mg every six hours and intravenous lorazepam 2mg every two hours were administered. Over 24 hours, despite 48mg of intravenous lorazepam, he continued to have disorientation, tremors, agitation, irrelevant speech, visual hallucinations, and sleep disturbance.

He was then transferred from the surgical ward to the de-addiction unit. He was placed in a quiet, well-lit room with a visible clock and calendar, and his vitals, hydration, and metabolic parameters were monitored and maintained. Lorazepam was titrated to 40 mg/day with some improvement in agitation, but irritability, tremors, hallucinatory behavior, disorientation, irrelevant speech, and sleep disturbances persisted. He showed frequent tachycardia (up to 110 beats/minute) and hypertension (up to 180/120mmHg), and the cardiologist advised intravenous labetolol 10mg every eight hours.

Persistent delirium led to neurology and intensive care unit consultations. In the absence of generalized tonic-clonic seizure (GTCS), possibility of nonconvulsive status epilepticus was kept and intravenous phenytoin 100mg eight hourly was started and midazolam 1mg/hour. Lorazepam and midazolam doses were titrated as per severity of agitation on Richmond Agitation Sedation Scale. Over the next two days, all symptoms improved. Midazolam was tapered off 50 percent per day and was discontinued completely by Day 6, and by Day 2, lorazepam was reduced 4mg every three hours until a dosage of 32mg was reached by Day 3. His vitals and electrolytes normalized, labetolol, calcium gluconate, and magnesium sulphate were tapered off and discontinued by Day 3. By Day 5, he had recovered completely. Lorazepam (32mg/day) and phenytoin (300mg/day) were shifted to oral doses.

Over the next three weeks, oral lorazepam followed by chlordiazepoxide were tapered off completely, and phenytoin was switched to levetiracetam 500mg twice daily, and thiamine 100mg twice daily and multivitamins were added. By the third week, disulfiram 250mg/day was started. Five sessions of relapse prevention counseling with him and his family were administered, focusing on future risk of lethal pancreatitis and DT. Pre-discharge assessment showed mild cognitive impairments. He was discharged after a 49 day de-addiction unit stay and remains in regular follow up, working as an agriculturist, and maintaining abstinence from alcohol and tobacco use for nine months.
DISCUSSION

DT carries a high fatality risk, and may require high level of monitoring and intensive care unit treatment.\[^{4}\] A physician’s preoccupation with physical comorbidities may result in the DT being overlooked in the early stages, which can worsen the outcome. However, proper recognition and prompt treatment can reduce the mortality from 1 to 5 percent to zero percent in different treatment settings.\[^{5}\]

Many risk factors for developing DT have been identified. One set includes acute physical comorbidity, recent heavy alcohol use, past history of DT or withdrawal seizures, severe withdrawal symptoms on presentation, age of 60 years or more, high blood alcohol levels, and poly substance abuse.\[^{3}\] Another set of risk factors includes current infectious disease, tachycardia (>120 beats/minute), signs of alcohol withdrawal accompanied by alcohol concentration of more than one gram per liter of body fluid, history of epileptic seizures, or delirious episodes.\[^{6}\] Additional risk factors are hyperthermia in first 24 hours of DT diagnosis (odds ratio [OR] 10.0), persistent tachycardia (OR 24.0), and the need for the use of restraints (OR 7.5).\[^{7}\] One retrospective study\[^{8}\] reported risk factors that include past history of DT (OR 3.99) and pulse rate greater than 100 beats/minute (OR 4.16), with rates for developing DT ranging from 20.4 percent with no predictor, 45.6 percent with one predictor, and up to 100 percent with two predictors. Our case had multiple risk factors for DT: past withdrawal seizures, high alcohol intake, pancreatitis, and tachycardia. Benzodiazepines are the drug of choice for managing DT, as other medications used for alcohol withdrawal (e.g., carbamazepine, magnesium sulphate) have either not been evaluated or have been found to be ineffective.\[^{9,10}\] Benzodiazepines can be administered by fixed-schedule (pre-specified doses and intervals) or symptom-triggered regimens (intervals and doses as per clinical severity or withdrawal rating scale scores).\[^{3}\] However, many patients are refractory to standard doses of benzodiazepines (e.g., 1600mg of lorazepam/24 hours).\[^{11}\] Strategies used in such cases include high doses/combinations of diazepam, lorazepam, midazolam, phenobarbbitone,\[^{10}\] fentanyl,\[^{12}\] and propofol.\[^{13}\] Our case had a failure of both: more than the standard doses of benzodiazepines recommended for alcohol withdrawal\[^{10}\] and the unconventional benzodiazepines (midazolam) to achieve adequate DT control. He required up to 266mg of lorazepam, equivalent doses of benzodiazepines, and use of phenytoin and labetalol. Use of propofol was ruled out by preexsiting pancreatitis, a known side effect and relative contraindication for the use of propofol, especially in high doses.\[^{13}\]
In our case, we used injectable haloperidol to manage agitation that persisted despite high doses of benzodiazepines. Neuroleptic agents, including the phenothiazines and haloperidol, demonstrate some effectiveness in reducing signs and symptoms of withdrawal, but these agents increase the incidence of seizures compared to placebo and are much less effective than benzodiazepines in preventing seizures that often complicate the clinical picture of DT. \[10\] Neuroleptic agents are widely used to calm agitated patients, and uncontrolled clinical experience indicates that neuroleptic agents are useful for this purpose in the setting of alcohol withdrawal as well.\[14\] However, benzodiazepines are the agents of choice in DT, and neuroleptics should be used with caution and only in intractable cases. In our case, severe behavioral abnormality precluded an electroencephalogram (EEG) preceding the use of intravenous phenytoin; however, improvement after phenytoin use renders it difficult to sift the relative role in the improvement of delirium vis-a-vis medications used for withdrawal state, metabolic derangements, or management of a possible underlying nonconvulsive status epilepticus. In the absence of generalized tonic-clonic seizures (GTCS) (commonly reported to be associated with DT, and in our case associated with alcohol withdrawal in the past), we concluded that the clinical picture was essentially of DT only. It is important to note that all previous reports of cases refractory to standard doses of benzodiazepines have come from intensive care units, and use of the recommended high doses in an outpatient or standard inpatient setting is generally not possible. However, our case was managed in the general ward of a de-addiction unit.

**CONCLUSION**
Highlights the fact that instead of always requiring intensive care unit care, severe DT may be successfully managed in a general ward, based on the application of the following approaches: early recognition; a multimodality, multispecialty treatment, and titration of the required benzodiazepines as per the clinical symptoms, including continuous infusion of benzodiazepines.

**REFERENCES**