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Unexpected clinical outcomes following the implementation of a standardised order set for hepatic encephalopathy

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ABSTRACT

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Correspondence to Dr Mandip KC; kcxxx011@umn.edu **Objective** We evaluated the effect on clinical outcomes of implementing a standardised inpatient order set for patients admitted with hepatic encephalopathy (HE). Methods A retrospective review of patients with cirrhosis admitted with HE. Hospital admissions for HE for which the electronic health record (EHR) order set was used were compared with admissions where the order set was not used. Primary outcome was length of hospital stay (LOS). Secondary outcomes were 30-day readmissions, inhospital complications, in-hospital and 90-day mortality. Results There were 341 patients with 980 admissions over the study period: 263 patients with 736 admissions where the order set was implemented, and 78 patients with 244 admissions where the order set was not implemented. Median LOS was 4 days (IQR 3-8) in the order set group compared with 3 days (IQR 2-7) (p<0.001); incidence rate ratio 1.37 (95% Cl 1.20 to 1.57), p<0.001, 30-day readmissions rate was 56% in the order set group compared with 40%, p=0.01; OR for readmission was 1.88 (95% Cl 1.04 to 3.43), p=0.04. Hypokalaemia occurred in 46% of admissions with order set use compared with 36%, when the order set was not used; p=0.003, OR 1.72 (95% CI 1.22 to 2.43), p=0.002. No significant differences were seen for in-hospital mortality and 90-day mortality.

Conclusion Implementation of an inpatient EHR order set for use in patients with HE was associated with unexpected clinical outcomes including increased LOS and readmissions. The convenience and advantages of standardisation of patient care should be balanced with a degree of individualisation, particularly in the care of medically complex patients. Furthermore, standardised processes should be evaluated frequently after implementation to assess for unintended consequences.

INTRODUCTION

Hepatic encephalopathy (HE) is a common complication of liver disease and patients with HE have high rates of healthcare utilisation.¹ Several studies have looked at the delivery of quality care to hospitalised patients with cirrhosis and have concluded that a low proportion of patients receive high quality care.^{2–5} In 2010, a set of quality indicators were derived by an expert panel with the intention of setting a platform for the delivery of quality care to patients with cirrhosis.⁶

Summary box

What is already known about this subject?

Standardised order sets are being increasingly used in delivery of care in hospitalised patients, but data are limited on their impact on patients with cirrhosis.

What are the new findings?

The implementation of a standardised electronic health record order set for patients admitted with hepatic encephalopathy at our institution was associated with unexpected clinical outcomes including increased hospital length of stay and increased 30day readmissions.

How might it impact on clinical practice in the foreseeable future?

The results from our study illustrate the challenges in standardising the care of medically complex patients in general, where good clinical judgement is irreplaceable to ensure successful clinical outcomes.

Electronic health records (EHRs) are now almost ubiquitous in the American healthcare systems. Order sets are clinical decision support tools that aim to help providers by reducing variability, ordering pre-specified doses of medications and promoting adherence to guidelines in the care of patients, often who have a specific condition or disease. The use of order sets has been proposed as one approach to improve quality care in cirrhosis.⁵ Standardised order sets have been shown to improve adherence to clinical guidelines in venous thromboembolism and stroke,⁷⁸ and improve clinical outcomes in the management of myocardial infarction and sepsis.^{9 10} One recent study looked at the development of an EHR order set to improve clinical outcomes in patients with variceal bleeding and demonstrated improvements in both the use and time to administration of antibiotics.¹¹

Even though there is clear evidence of the benefits of order set use, there are also cautionary examples of their potential drawbacks on patient outcomes and healthcare utilisation. One study showed that a higher proportion of patients were exposed to increased risk of harm following the implementation of a standardised order set for venous thromboembolism prophylaxis.¹² Overuse of medications such as sleeping aids, inappropriate longterm proton-pump inhibitor use and overuse of telemetry in the hospitalised setting have also been identified as unintended consequences of order set use.^{13–15}

The effect of order set use on clinical outcomes on patients with cirrhosis and HE is unknown. We aimed to evaluate utilisation of an inpatient order set derived for use in patients with cirrhosis admitted to the hospital with HE and to evaluate the impact on clinical outcomes.

METHODS Setting

The University of Minnesota Medical Center (UMMC) is a tertiary care medical centre with a high-volume liver transplant programme in the upper mid-western USA. Depending on patient acuity, patients with cirrhosis are admitted to either a Hospital Medicine team—staffed by a hospitalist with or without internal medicine residents—or the intensive care unit (ICU). An EHR (EPIC, Verona, Wisconsin, USA) was implemented at UMMC for use in the inpatient setting in 2011. The HE order set was developed and made available for use at UMMC in December 2013. It is available (and encouraged) for use by all providers at any time during an admission and incorporates standardised pre-checked orders for the management of HE including a nursedriven lactulose protocol, which involves nursing assessment of a patient's mental status based on West Haven criteria.¹⁶ The order set includes a brief summary of stages of HE and frequent nursing assessment of HE severity. The presence of HE results in administration of 20g lactulose orally, or 100g lactulose rectally, every 2 hours as needed until resolution of symptoms. The content of this order set is consistent with evidence-based, standard practices in the management of HE.¹⁶

In addition, the order set also includes pre-checked orders for laboratory and medication orders for rifaximin, as well as options to order radiology studies and electrolyte replacement (figure 1). Of note, this order set was developed and implemented prior to conceptualisation and conduction of this study. This study was conducted with the approval of the University of Minnesota Institutional Review Board.

Study design

We performed a single centre, retrospective review of EHR data of the patients with cirrhosis admitted to

Drder Sets	Clear All Orders T DIAGNOSTIC IMAGING
AED Henatic Encenhalonathy Focused ADUIT & Personalize * &	▼ Diagnostic Imaging
	XR Chest 2 Views (\$)
Version: 2016-Dec-14 (3041011029)	US Abdomen Complete (\$\$\$)
PATIENT CARE	
▼ Nursing	▼Consults - UU,UR
Strict intake and output	Gastroenterology Adult IP Consult PANEL
Mini-Mental Status Exam	Physical Therapy Adult IP Consult
LABORATORY	Cocupational Therapy Adult IP Consult
▼Routine - Lab Collect On Admission - UU,UR	Transplant SW: if listed for a transplant.
Suggested collection of BMP if not drawn upon ED admission.	DUADMACY MED Heastic Encentral anothy Encured ADULT
CBC with platelets differential (\$\$)	Medication Exclusions
	No benzodiazepines
Basic metabolic panel (SS) ROUTINE	Daily 2 GRAM acetaminophen limit, unless fulminent liver failure or transaminases greater than or equal to 300 - 400, then none Daily 2 GRAM acetaminophen limit, unless fulminent liver failure or transaminases greater than or equal to 300 - 400, then none
Hepatic panel (\$\$) ROUTINE, Albumin, Alk Phosphatase, ALT, AST, Bilirubin (Conjugated, Delta, Total), Total Protein	
INR and PTT Panel	550 mg, Oral, 2 TIMES DAILY, May give per NG if patient unable to take PO Indications: Intestinal bacteria reduction in the treament of Hepatic Encephalopathy
Magnesium (\$\$)	Hepatic Encephalopathy Nurse Initiated Treatment, Adult Acute Care - UU,UR,UA Any time symptoms of Hepatic Encephalopathy are noted. DN to implement Lachildee Nurse Initiated exclosed using the Most House Straine
ROUTINE Phosphorus (\$)	Any time symptoms or reparic complication and the notes, risk to implement acculose known manage protocol using inerview haven saging Assessment. If symptoms of Hepatic Encephalopathy recurs differ providely receiving with treatment. RN will re-implement the protocol. RN to notify the primary team each time the Hepatic Encephalopathy rours initiated protocol is implemented.
ROUTINE	West Haven Staging Assessment Stage 1: Confused, shortened attention span, sleep disturbance, altered mood.
ROUTINE, IF concerns of Pancreatitis.	Stage 2: Increased drowsiness; disorientation; inappropriate behavior; mood swings; agitation.
Lipase (\$\$)	Stage 3: Somnolence; difficult to rouse; sleeps most of time; marked confusion; incoherent speech. Obeying only simple commands.
ROUTINE, IF concerns of Pancreatitis.	Stage 4: Comatose; may not respond to painful stimuli.
Blood culture (\$\$) ROUTINE	Nurse Initiated Lactulose Protocol Routine (FFECTIVE NOW), stanting today at 1115, Unit) Specified Nurse Initiation (Strength State) (State) (State
Alcohol ethyl: Blood (\$\$) CUTINE, Blood	why time by injunction or reglate. Despendapping forg all ended, his so injutement is classicate invase instabutions or products in symptomic to the local and periodicity resolving with treatment, bit mile implement the portocicit. We can only the primary terms during the functional instabution to the Cost and and Stages Stage. To only add, shortened attention span, steep disclustance, altered mood Stage 2: Increased downees, disconstration (impapporate behavior) mo avoing agattation, Stage 3: Somonetered difficult to rouge steeps more of the time, marked contralised interpretation commands. Stage
Drug Screen Panel - UU, UR, UA	4: Comatose may not respond to painful stimuli.
ABO/Rh type and screen (\$\$\$) ROUTINE	Assess Hepatic Encephalopathy (HE) West Haven staging assessment (stages 1-4) Routine, PER UNIT ROUTINE, starting today at 1115, Unit Specified Q4 hours if nor HE, bur need to assess Q2 hours if HE found.
Routine - AM Lab Collect Daily	Isctulose (CHRONULAC) solution 20 g (\$)
Suggested collection of CBC if not drawn upon ED admission.	20 g. Gral or NG Tube, 3 TIMES DAILY, First Dose today at 1400
CBC with platelets differential (SS) DAILY, AM DRAW	■ Lactuose Ciral or Rectal lactulose (CHRONULAC) solution 20 g (\$)
DAILY, AM DRAW	20.9, Unit of No. Lobe, EVENT 2 PULVICE YAV, why time symptoms of negative processing optimizers of the memory of the implement activation vursion interaction. Protocol: If symptoms of HE recur, RN will re-implement the protocol. RN to notify primary team each time HE Nurse Initiated Protocol is implemented, Starting today at 1102
Phosphorus (\$) DAILY, AM DRAW	For Stage 2 symptomic lactudose 20 g 100 mL) VOI No every 2 kris x 3 does. For Stage 2 symptomic lactudose 20 g 100 mL) VOI No every 2 kris x 3 does for refeating PO/ING, RECTAL (150 mL Lactudose mixed with 35 mm I KSWater and retained RECTALLY for 30 to 00 mL in a vectal table every 2 kris x 3 does for Stage 3 symptoms: lactudose 20 g (30 mL) PO/ING every 2 kris x 3 does or if refusing PO/ING, RECTAL (150 mL lactudose mixed with 350 mL NS/water and
Sodium (\$)	retained RECTALLY for 30 to 60 min via rectal tube) q 2 hrs x 3 doses. For Stages 1, 2, and 3: After 6 hours of treatment, if symptoms have improved back to baseline, revert to scheduled Lactulose dos. If symptoms have remained stable or progressed, discuss with primary medical team continuing current plan u outliest descent and stables and stables and stables and a lacture and a lacture and a lacture stable stables and
	parient clears mentally, For Stage 4 Symptoms: lactulose 20 g (20 mL) No every 2 hours unit patient clears mentally OR RECTAL (150 mL lactulose mixed wi 350 mL NS/water and retained RECTALLY for 30 to 60 min via rectal tube) g 2 hrs until patient clears mentally. After 6 hours of treatment, if symptoms have
DAILY, AM DRAW	remained stable, discuss with primary medical team continuing current plan until patient clears mentally. Or
▼ Routine AM Lab Collect 3 times per week	lactulose (CHRONULAC) solution for enema prep 100 g (\$\$)
Hepatic panel (\$\$) EVERY MWF, AM DRAW	100 g, Rectal, EVERY 2 HOURS PRN, Any time symptoms of HEI/H3 are noted, RN to implement Lauritude Nurse Initiated Protocol. If is symptoms of H4 recur, will re-implement the protocol. RN to notify primary team exist initia HE Nurse Initiated Protocol is implemented. Suthing today at 1102 For Stage 2 Symptoms: lactudose 20 g (20 ml) POING every 2 hrs x 3 doses or if reliaring POING, RECTAL (150 mL lactudose mixed with 350 mL NS/water ar
▼ Routine - PCU Collect	resamed kts. LALLY for sU to oU min via rectar tubej every 2 mis x s doses. After o hours of treatment, it symptoms have improved back to baseline, revert to scheduled lactulose dose. If symptoms have remained stable or progressed, discuss with primary medical team continuing current plan until patient clears
UA with Microscopic (\$) Urine	mentally, for Stage 3 Symptoms RECTAL (150 mL bachlose mixed with 350 mL NS/water and retard RECTALLY for 30 to 60 min via rectail tubbe every 2 h 3 doors. If patient worsens (ex. becomes comatose) call an RRT and alert Primary team of decline of patient status, now requiring ICU monitoring. After 6 h of treatment, if synchrons have remained stable, discuss with primary medical team continuing current plan until patient clears mentally. For Stage 4
Urine Culture Aerobic Bacterial (\$\$) Urine	Symptoms RETAL (150 mL lackboor enixed with 30 mL KN-state and realized RETALLY for 20 to 60 min via retait bab) every 2 hrs until patient clears mentally OR Lackboor (20 gO mL) NG every 2-hous with planter clears mentally. After 6 hours of treatment, if symptoms have remained stable, discuss w primary medical team continuing current plan until patient clears mentally.
Fluid Culture Aerobic Bacterial: Peritoneal Fluid (\$\$) ROUTINE, Peritoneal Fluid	Thiamine and Folic Acid Click for Determine Public generation of "Link" contractions to the with current MCCP LTCP that Acid Click for
▼ Paracentesis Labs	mL/min Cick for h
**Provider Instruction- To order a paracentesis order set refer to- IR RAD Paracentesis PRE PROCEDURE order set	t. Magnesium Replacement - select "Standard" or "High" replacement option " Use with caution if GFR less than 30 Click for n
Albumin level (5) ROUTINE	mu,min ♦ Phosphorus Replacement - select "Standard" or "High" replacement with POTASSIUM or SODIUM Phosphate option * Click for m Use with caution if GFR less than 30 mL/min
Gram stain (\$)	Additional Order Set Orders
Fluid Culture Aerobic Bacterial (\$\$)	⊘ Search
ROUTINE	You can search for an order by typing in the header of this section.

Figure 1 Hepatic encephalopathy order set.

Table 1 Baseline characteristics			
	Order-set used n=263	Order-set not used n=78	P value
Female, n (%)	108 (41)	27 (35)	0.31
Caucasian race, n (%)	204 (84)	64 (86)	0.55
Age, mean (SD)	56.0 (10.5)	58.9 (11.3)	0.05
MELD, mean (SD)	20.7 (8.5)	21.0 (7.2)	0.79
MELD-Na, mean (SD)	19.7 (10.2)	21.3 (8.4%)	0.20
Aetiology of liver disease			0.22
Alcohol, n (%)	113 (45)	27 (35)	
Hepatitis C, n (%)	28 (11)	14 (18)	
Alcohol and hepatitis C, n (%)	28 (11)	7 (9)	
Other, n (%)	81 (32)	29 (38)	
Comorbid conditions			
CKD, n (%)	60 (23)	12 (15)	0.16
ESRD, n (%)	14 (5)	4 (5)	1.00
HIV, n (%)	1 (0.4)	1 (1)	0.41
Diabetes, n (%)	104 (40)	27 (35)	0.43
COPD, n (%)	20 (8)	8 (10)	0.45
Coronary artery disease, n (%)	21 (8)	7 (9)	0.78
No. of hospital encounters, n	736	244	
Rifaximin use, n (%)	712 (97)	203 (83)	<0.001
Precipitant of HE			0.13
Medication non-adherence, n (%)	247 (34)	80 (33)	
Unknown precipitant, n (%)	128 (17)	64 (23)	
GI bleed, n (%)	33 (4)	13 (5)	
Urinary tract infection, n (%)	76 (10)	13 (5)	
Spontaneous bacterial peritonitis, n (%)	44 (6)	13 (5)	
Other, n (%)	208 (28)	70 (29)	

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; GI, Gastrointestinal; HE, hepatic encephalopathy; MELD, model of end-stage liver disease.

UMMC with HE from December 2013 to December 2017. Hospital admissions for which the EHR order set was used at hospital admission were compared with admissions where the order set was not used.

Study outcomes

The primary outcome was hospital length of stay (LOS). Secondary outcomes were 30-day readmissions, in-hospital complications, in-hospital mortality and 90-day mortality. In-hospital complications included hypernatraemia (defined as serum sodium >145 mEq/L or an increase in serum sodium >5 mEq/L at any point in the hospital admission); hypokalaemia (defined as serum potassium <3.5 mEq/L at any point in the admission) and acute kidney injury (defined as an increase in serum creatinine >0.3 mg/dL over 48 hours).

Study population

Patients were included in the study if they were admitted to the UMMC Hospital Medicine service with

an International Classification of Diseases-Ninth Revision (ICD-9) or ICD-10 code for cirrhosis and HE or altered mental status in admission or discharge coding. All admissions for HE were validated by manual chart review by a single physician in accordance with the definition of HE provided in the current American Association for the Study of Liver Diseases practice guideline.¹⁶ Patients with a diagnosis code for HE that did not meet criteria for HE after chart review were excluded from this study.

Patients were also excluded if they were less than 18 years old; if they had previously received a liver transplant; if they were originally admitted for non-HE condition; if they were admitted to the ICU or any other service than Hospital Medicine; if they were admitted for another acute neurological condition (cerebrovascular accident, meningitis, acute intoxication, intracranial haemorrhage or seizure) or if they were placed on comfort care/ hospice care during their hospitalisation.

Data acquisition

Patient demographics (age, gender, ethnicity); hospitalisation data (admission and discharge dates, hospital readmission data, hospital admission unit); laboratory values; medications; co-morbid conditions and order-set utilisation data were obtained from the University of Minnesota Clinical and Translational Science Institute's clinical data repository via their Informatics Consulting Service. Aetiology of liver disease and precipitating factor for HE was obtained by manual chart review by a single physician.

Statistical analysis

Descriptive statistics were calculated and presented by group. Mean and SD were presented for continuous variables that are normally distributed. Median and IQR were presented for length of stay and number of readmissions as their distribution was skewed. Frequency and percentage were presented for categorical variables.

Bivariate analysis was conducted to compare order set use versus standard care using two-sample t-test for continuous variables that were normally distributed, nonparametric Wilcoxon test for length of stay and number of readmissions and χ^2 test (or Fisher's exact test if any cell count was less than 5) for categorical variables. Multivariate analysis was performed to examine the effect of order set use on patient outcomes, adjusting for patient demographics including age at first HE episode, gender, race, aetiology of liver disease, rifaximin use and precipitant for HE. These covariates were selected based on scientific rationale as clinical factors known to affect clinical outcomes in patients with HE. Negative binomial regression models were conducted for length of stay and number of readmissions, and incidence rate ratio (IRR) was presented. Logistic regression model was conducted for binary outcomes, and OR was presented. Analyses were performed in SAS V.9.4 (SAS Institute). P values <0.05 were considered statistically significant.

 Table 3
 Adjusted risk for clinical outcomes with regard to order set use

		P value
Hospital length of stay	IRR 1.37 (95% CI 1.20 to 1.57)	<0.001
30-day readmissions	OR 1.88 (95% CI 1.04 to 3.43)	0.04
Complications		
Hypernatraemia	OR 1.19 (95% CI 0.86 to 1.66)	0.11
Hypokalaemia	OR 1.72 (95% CI 1.22 to 2.43)	0.002
Acute kidney injury	OR 1.31 (95% CI 0.94 to 1.85)	0.11
90-day mortality	OR 1.02 (95% CI 0.55 to 1.89)	0.95

Outcomes adjusted for age, gender, race, aetiology of liver disease, rifaximin use and precipitant for hepatic encephalopathy. IRR. incidence rate ratio.

IRR, incidence rate ratio

RESULTS Baseline characteristics

There were a total of 341 unique patients with 980 admissions over the study period: 263 unique patients with 736 admissions where the order set was implemented, and 78 unique patients with 244 admissions where the order set was not implemented. Patients in the group where the order set was not used were older compared with the group where the order set was used (mean age 58.9 years vs 56.0 years, p=0.05). Alcohol-related cirrhosis was the most common aetiology of liver disease in both groups. The mean model of end-stage liver disease (MELD)/ MELD-Na was 20.9/20.5 for the entire cohort. No significant differences were observed between the two groups for gender, ethnicity, mean MELD/MELD-Na score, co-morbidities, aetiology of liver disease or precipitant of HE. Rifaximin was used in 97% of patient encounters when order set was used compared with 83% when the order set was not used, p<0.001. The most common documented

Table 2 Unadjusted clinical outcomes comparing patients with and without order set use						
	Order set used n=263	Order set not used n=78	P value			
Total no. of admissions, n	736	244				
Length of stay, median (IQR)	4 (3–8)	3 (2–7)	<0.001			
No. of readmission within 30 days, median (IQR)	1 (0–3)	0 (0–1)	0.001			
Readmitted within 30 days of previous discharge, n (%)	148 (56)	31 (40)	0.01			
Complications						
No. of encounters with hypernatraemia, n (%)	379 (51)	108 (44)	0.05			
No. of encounters with hypokalaemia, n (%)	341 (46)	87 (36)	0.003			
No. of encounters with AKI, n (%)	342 (47)	102 (42)	0.19			
In-hospital mortality	5 (2%)	1 (1%)	1			
90-day mortality	93 (35%)	23 (29%)	0.34			

AKI, acute kidney injury.

HE precipitant was medication non-adherence. Despite extensive manual chart review, a large number of admissions had an unknown precipitant (table 1).

Primary outcome

The median LOS for admissions where the order set was used was 4 days (IQR 3–8 days) compared with 3 days (IQR 2–7 days) for admissions where the order set was not used (p<0.001). After adjustment for age, gender, race, aetiology of liver disease, rifaximin use and HE precipitant, the incidence rate for increased LOS for the order set use group was 37% higher than the incidence rate for the group which did not use the order set (IRR 1.37 (95% CI 1.20 to 1.57), p<0.001) (tables 2 and 3).

Secondary outcomes

Thirty-day readmissions were more common in the order set group, 56% vs 40%, p=0.01. The median number of readmissions was 1 (IQR 0–3) for admissions where the order set was used compared with 0 (IQR 0–1) when the order set was not used (p=0.001). After adjustment for age, gender, race, aetiology of liver disease, rifaximin use and HE precipitant, the OR for readmission in patients within 30 days for whom the order set was used was 1.88 (95% CI 1.04 to 3.43), p=0.04 (tables 2 and 3).

With regard to in-hospital complications, hypernatraemia occurred in 51% of admissions where the order set was used compared with 44% when the order set was not used, p=0.05; OR 1.19 (95% CI 0.86 to 1.66), p=0.11, on multivariate analysis. Hypokalaemia occurred in 46% of admissions using the order set compared with 36% of admissions that did not use the order set, p=0.003; OR 1.72 (95% CI 1.22 to 2.43), p=0.002, on multivariate analysis. Acute kidney injury did not vary depending on order set usage, 47% vs 42%, p=0.19; OR 1.31 (95% CI 0.94 to 1.85), p=0.11, on multivariate analysis (tables 2 and 3).

In-hospital mortality was 2% for admissions using the order set compared with 1% for those not using the order set but this did not reach statistical significance, p=1. Multivariate analysis was unable to be performed for in-hospital mortality due to the low number of deaths. Ninety-day mortality was 35% for admissions using the order set compared with 29% for admissions not using the order set, p=0.34; OR 1.02 (95% CI 0.55 to 1.89), p=0.95, on multivariate analysis (tables 2 and 3).

DISCUSSION

HE is a common complication of cirrhosis for which hospital admissions are increasing, making it an ideal target for the implementation of a standardised order set.¹⁷ However, the pathogenesis of HE is complex and remains poorly understood—and in our study, poorly documented. HE is a syndrome with several causes including infection and medication non-adherence; a recent study showed that 40%–76% of patients admitted with HE had multiple concurrent precipitants.¹⁸ With the fragility of patients with decompensated cirrhosis in general, careful assessment and management of all patients admitted to hospital with HE is essential.

Standardised EHR order sets have been proposed as one solution to address the current deficit in quality care delivered to patients with cirrhosis.^{2–5} In our study, despite high utilisation of an inpatient EHR order set for HE, order set use was associated with increased hospital LOS and 30-day readmissions in this study. These findings persisted on multivariate analysis and demonstrate the difficulty in adopting standardised order sets in the care of medically complex patients. It does not appear that patients for whom providers opted to use the order set were significantly clinically different than those patients in whom the order set was not used.

Adherence to standardised order sets can have unin-tended outcomes in patient care.^{12-15 19} Our findings contribute to an emerging body of literature describing the limitations of order set use and demonstrate the importance of critical thinking in patient care, particularly in a patient population as susceptible to harm as those with cirrhosis.²⁰ HE is a syndrome—not a single entity—and careful, expert attention to the underlying precipitants as well as the recognition of the potential adverse effects of any intervention is fundamental. Certainly, medication non-adherence is a common precipitant-and lactulose is required in majority of patients admitted with HE. However, a diagnostic and treatment approach that lacks nuanced tailoring to a specific patient's presentation can be problematic. While order sets can reduce unnecessary variation in care, a degree of individualisation may be necessary in the management of these complex patients; in fact, order sets could be modified to encourage such assessment and individualisation.

One possible explanation for our findings is that the increased rate of complications observed in the order set group would logically lead to both increased hospital LOS and 30-day readmissions. Order set use was significantly associated with hypokalaemia-a known side effect of lactulose overuse-which may appear innocuous at first glance. However, hypokalaemia has been shown elsewhere to increase hospital and ICU lengths of stay in patients with HE.²¹ Moreover, hypokalaemia is associated with increased all-cause mortality in the elderly and in patients with chronic kidney disease (CKD).^{22 23} We also observed trends for increased rates of hypernatremia and acute kidney injury, both of which are more traditionally associated with poor clinical outcomes in patients with cirrhosis.^{24 25} There are multiple possible explanations for these findings, but we posit that patients treated with the order set were treated more aggressively with lactulose. Overuse of diuretics may have contributed to the increased rates of hypokalaemia and acute kidney injury seen in the order set group-and indeed may even account for a significant proportion of the 'unknown' HE precipitants in the whole cohort-but would not explain the higher rates of hypernatraemia. Administration of lactulose is the foundation of the treatment of HE but can have significant side effects including hypovolaemia,

hypokalaemia and metabolic acidosis. It is possible that our order set was too aggressive in the administration of lactulose, particularly given the high rate of comorbidities (especially CKD and diabetes) in our patient population. Our outcomes may also have been a reflection of the high mean MELD-Na score at admission in our cohort, which in itself has been associated with higher readmission rates, although a significant difference was not observed between the two study groups.²⁶⁻²⁸

On a positive note, we observed higher rates of rifaximin use in the order set group. Although not a specific outcome of our study, rates of rifaximin use were high in both groups but significantly higher in the order set group. Rifaximin is a non-absorbable antibiotic that has been shown to reduce the risk of development of HE and improves quality of life outcomes in patients with cirrhosis.^{29 30} In a recent metaanalysis, the use of rifaximin was associated with reduced overall mortality in patients with HE.³¹ Despite increased rifaximin use, we did not observe any improvement in mortality in the order set group: this may again be a reflection of higher baseline MELD-Na in our cohort but may also be due to the exclusion of patients admitted to the ICU from our study.

As our study groups were not randomised, it is important to consider why the order set was used in some encounters and not others. Both groups were similar with the exception of slightly older age in the order set group, which was not large enough to account for the difference in outcomes. Reasons for non-utilisation of order sets may include provider preference, lack of awareness of order set and lack of mandatory implementation within a health system.^{32 33} In this study, it is possible that use of the order set was affected by providers' perceived loss of control with regard to the nurse-driven lactulose protocol. The remainder of the content of the order set was consistent with standard, evidence-based practices and was unlikely to have contributed to these concerns.

Our study is the first to evaluate the implementation of an EHR order set in patients admitted to hospital with HE. Our findings are important due to their unexpected nature and illustrate the difficulty encountered in improving the quality of care in patients with decompensated cirrhosis. Hospital length of stay and 30-day readmissions are well-described metrics for resource utilisation which have significant financial implications.^{34 35} Increased hospital length of stay and readmissions have been shown both to increase the cost of care and worsen clinical outcomes in patients with decompensated cirrhosis.^{26 36} This is particularly relevant at a time when healthcare costs are spiralling out of control in the USA: hospitalisation costs for patients with cirrhosis increased by 30% to \$7.37 billion in 2014.³⁷

The strengths of our study include a large number of patients and patient encounters. Manual review of our data ensured accuracy and granularity, particularly with regard to HE precipitant which can be difficult to elucidate with automated data collection. The 4-year study period also accounted for any lag that can be occur following the implementation of EHR order set due to 'late adopters'. Limitations of our study include the single centre, retrospective design which may limit the generalisability of our results. Second, it can be difficult to capture all readmissions to a tertiary care referral hospital as patients often re-present to other institutions. Third, a large number of HE precipitants in our study were deemed 'unknown' despite extensive evaluation; however, this is a reflection of real-world practice. Finally, we acknowledge that patients with more severe HE at presentation may have preferentially had the order set used in their care. However, it is difficult to fully account for this possibility in our study: the West Haven criteria have significant intra-operator and inter-operator variability, and the mental status of patients with significant liver disease can fluctuate markedly.³⁸ Again, we note that there was no significant difference in baseline liver function, represented by the MELD-Na score on admission, between the two study groups.

In conclusion, the implementation of a standardised EHR order set for patients admitted with HE at our institution was associated with unexpected clinical outcomes including increased hospital LOS and increased 30-day readmissions. The results from our study illustrate the challenges in standardising the care of medically complex patients in general, where good clinical judgement is irreplaceable to ensure successful clinical outcomes. Moreover, attempts to standardise care should be carefully monitored for adverse effects. Further study is required to understand why providers may opt out of using order sets and to optimise the utilisation of EHR to improve the quality of care delivered to patients with cirrhosis in hospital.

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