

Utility of the Hepatic Encephalopathy Scoring Algorithm (HESA) for Diagnosing Hepatic Encephalopathy in a Randomized, Controlled Trial of Rifaximin vs. Placebo

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INTRODUCTION

- The Conn score (West Haven criteria) is widely used as a grading system for assessing the severity of hepatic encephalopathy (HE)¹
 - Although clinically simple, limitations include subjectivity of healthcare provider interpretation, lack of specific definitions for each grade, and inaccuracy in differentiating milder grades of HE severity²
- The Hepatic Encephalopathy Scoring Algorithm (HESA) is an adaption of this grading system; HESA combines clinical examination with standardized and validated indicators of cognitive impairment to improve objectivity and increase sensitivity for determining HE severity (Figure 1; Table 1)³
 - Designed to minimize effects of patient age and education level^{2,4}
 - Relies primarily on clinical examination for more severe HE (ie, grades III-IV), in which neuropsychological testing is not feasible, and on objective cognitive testing for less severe HE (ie, grades I-II)^{2,3}
- HESA was incorporated into a large, randomized, placebo-controlled trial of rifaximin 550 mg twice daily for the maintenance of recurrent HE remission⁵

Figure 1. Hepatic Encephalopathy Scoring Algorithm (HESA)

HE Grade	Clinical Assessments	Neuropsychological Assessments	HE Grade Determination
IV	<ul style="list-style-type: none"> No eyes open No verbal response No reaction to simple commands 	<ul style="list-style-type: none"> Not applicable 	All 3 indicators present
III	<ul style="list-style-type: none"> Somnolence Confusion Disoriented to place Bizarre behavior/anger/rage Clonus/rigidity/nystagmus/Babinski 	<ul style="list-style-type: none"> Mental control = 0 	At least 3 indicators present, either clinical or neuropsychological
II	<ul style="list-style-type: none"> Lethargy Disoriented to time Slurred speech Hyperactive reflexes Inappropriate behavior 	<ul style="list-style-type: none"> Slow responses Anxiety Amnesia recent events Simple computations 	At least 2 clinical and 3 neuropsychological indicators present
I	<ul style="list-style-type: none"> Sleep disorder Tremor 	<ul style="list-style-type: none"> Complex computations Construction ability Shortened attention span Depression 	At least 4 indicators present, either clinical or neuropsychological

Scoring begins with the highest HE grade (grade IV) working downward through the algorithm. Clinical assessments are indicated by (●) and neuropsychological assessments are indicated by (■). Adapted with permission from Hassanein T et al. *Am J Gastroenterol.* 2009;104(6):1392-1400.

Table 1. Indicators of Impairment on Neuropsychological Measures

Neuropsychological Assessment	Impairment
HESA grade III	Mental control
HESA grade II	Slow responses Anxiety Amnesia recent events Simple computations
HESA grade I	Complex computations Construction ability Shortened attention span Depression

BVMT-R = brief visuospatial memory test-revised; HVLTL = Hopkins verbal learning test. Adapted with permission from Hassanein TI, Hilsabeck RC, Perry W. *Dig Dis Sci.* 2008;53(2):529-538.

OBJECTIVE

- To assess the utility of the HESA as a tool for enhancing HE grading in randomized, controlled trials

METHODS

- This was a randomized, phase 3, placebo-controlled, multinational clinical trial in adults with cirrhosis and HE who were currently in remission (Conn score 0 or 1) and had a history of ≥2 episodes of overt HE (Conn score ≥2) within 6 months of screening⁵
- HESA was used to assist in assigning Conn score at clinic visits⁵
 - Aid for detecting "subtle" breakthrough HE episodes during clinic visits
 - HESA and Conn assessments at a particular visit were to be performed by the same individual whenever possible
 - Clinic visits occurred on days 7 and 14 and every 2 weeks thereafter through day 168 (end of the treatment), with optional visits on days 42, 70, 98, 126, and 154
- A breakthrough overt HE episode was defined as an increase in Conn score to grade ≥2, or if baseline Conn score = 0, an increase of 1 grade each in Conn and asterixis scores⁵
- This post hoc analysis evaluated the ability of HESA parameters to differentiate HE Conn scores at baseline and post-baseline

RESULTS

Patient Disposition and Demographics

- A total of 299 patients were treated at 70 centers in North America and Russia (Table 2)⁵
 - Baseline HESA data were available for 129 patients with a Conn score of 0 and 43 patients with a Conn score of 1

Table 2. Demographics and Baseline Disease Characteristics

Characteristic	All patients (N = 299)
Age (years), mean (SD)	56.2 (9.4)
Male, n (%)	182 (60.9)
Race, white, n (%)	257 (86.0)
Time since advanced liver disease diagnosis (months), mean (SD)	56.2 (58.2)
Duration of current HE remission (days), mean (SD)	71.1 (49.6)
Conn score, n (%)	
0	200 (66.9)
1	99 (33.1)
Model End-Stage Liver Disease (MELD) score, n (%) ^a	
≤10	82 (27.4)
11-18	190 (63.5)
19-24	26 (8.7)
Country	
United States	205 (68.6)
Russia	80 (26.8)
Canada	14 (4.7)

^aData missing for 1 patient.

RESULTS

- Significant differences were observed at baseline between patients with a Conn score of 0 versus those with a Conn score of 1 for 2 clinical HESA indicators ($P < 0.001$) and 4 neuropsychological HESA indicators ($P < 0.05$; Table 3)

Table 3. Impairment According to HESA Indicators, by Baseline Conn Score

HESA Indicator, n (%) ^a	Conn score = 0 (n = 129)	Conn score = 1 (n = 43)	P value ^b
HESA grade II			
Clinical			
Lethargy	10 (7.8)	2 (4.7)	NS
Disoriented to time	1 (0.8)	2 (4.7)	NS
Slurred speech	1 (0.8)	2 (4.7)	NS
Hyperactive reflexes	1 (0.8)	2 (4.7)	NS
Inappropriate behavior	0	0	—
Neuropsychological			
Slow responses	18 (14.0)	9 (20.9)	NS
Anxiety	17 (13.2)	10 (23.3)	NS
Amnesia of recent events	64 (49.6)	32 (74.4)	0.005
Simple computations	4 (3.1)	6 (14.0)	0.02
HESA grade I			
Clinical			
Sleep disorder	32 (24.8)	27 (62.8)	< 0.001
Tremor	17 (13.2)	21 (48.8)	< 0.001
Neuropsychological			
Complex computations	31 (24.0)	18 (41.9)	0.03
Construction ability	3 (2.3)	1 (2.3)	NS
Shortened attention span	10 (7.8)	5 (11.6)	NS
Depression	17 (13.2)	13 (30.2)	0.02

^aWith the exception of mental control = 0 (6 patients with Conn score = 0 and 3 patients with Conn score = 1, $P = 0.70$), ≤1 patient showed impairment in HESA clinical indicators for HE grades III or IV.

^bConn score of 0 vs 1.

NS = not significant; $P > 0.05$.

- During clinic visits, 18 patients were identified as having progressed to a Conn score = 2, indicative of a breakthrough HE episode
- Significant differences were observed for several HESA clinical and neuropsychological indicators post-baseline, most often between patients with a Conn score of 0 versus 2 or Conn score of 0 versus 1 (Table 4)
- There was generally good reliability among study sites consistent with prior findings⁴

RESULTS

Table 4. Impairment According to HESA Indicators, by Post-baseline Conn Score

HESA Indicator, n (%) ^a	Conn score = 0 (n = 138)	Conn score = 1 (n = 93)	Conn score = 2 (n = 18)	P value		
				0 vs 1	1 vs 2	0 vs 2
HESA grade III						
Clinical						
Somnolence	0	0	0	—	—	—
Confusion	0	0	1 (5.6)	—	NS	NS
Disoriented to place	0	1 (1.1)	0	NS	NS	—
Bizarre behavior/anger/rage	1 (0.7)	2 (2.2)	0	NS	NS	NS
Clonus/rigidity/nystagmus/Babinski	1 (0.7)	1 (1.1)	1 (5.6)	NS	NS	NS
Mental control = 0	6 (4.3)	7 (7.5)	4 (22.2)	NS	NS	0.02
HESA grade II						
Clinical						
Lethargy	8 (5.8)	25 (26.9)	14 (77.8)	< 0.001	< 0.001	< 0.001
Disoriented to time	1 (0.7)	4 (4.3)	3 (16.7)	NS	NS	0.005
Slurred speech	3 (2.2)	7 (8)	8 (44)	NS	< 0.001	< 0.001
Hyperactive reflexes	1 (0.7)	0	1 (5.6)	NS	NS	NS
Inappropriate behavior	0	2 (2.2)	10 (55.6)	NS	< 0.001	< 0.001
Neuropsychological						
Slow responses	46 (33.3)	28 (30.1)	10 (55.6)	NS	NS	NS
Anxiety	25 (18.1)	34 (36.6)	9 (50.0)	0.002	NS	0.005
Amnesia of recent events	94 (68.1)	59 (63.4)	15 (83.3)	NS	NS	NS
Simple computations	11 (8.0)	13 (13.9)	6 (33.3)	NS	NS	0.006
HESA grade I						
Clinical						
Sleep disorder	31 (22.4)	54 (58.1)	9 (50.0)	< 0.001	NS	0.02
Tremor	33 (23.9)	45 (48.4)	8 (44.4)	< 0.001	NS	NS
Neuropsychological						
Complex computations	38 (27.5)	44 (47.3)	9 (50.0)	0.003	NS	NS
Construction ability	7 (5.1)	12 (12.9)	2 (11.1)	0.049	NS	NS
Shortened attention span	20 (14.5)	19 (20.4)	6 (33.3)	NS	NS	NS
Depression	20 (14.5)	27 (29.0)	7 (38.9)	0.01	NS	0.02

^aNo patients showed impairment in HESA clinical indicators for grade IV. NS = not significant; $P > 0.05$.

CONCLUSIONS

- HESA provided good precision in differentiating Conn scores 0 from scores of 1 or 2 and is a time-efficient, objective, and reliable approach for assessing the broad spectrum of neurologic and clinical manifestations of HE
- Although further validation is needed, HESA may provide a more objective assessment of HE severity than Conn score (West Haven) in multicenter clinical trials

REFERENCES 1. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. *Hepatology.* 2002;35(3):716-721. 2. Sakamoto M, Perry W, Hilsabeck RC, Barakat F, Hassanein T. *Clin Liver Dis.* 2012;16(1):27-42. 3. Hassanein TI, Hilsabeck RC, Perry W. *Dig Dis Sci.* 2008;53(2):529-538. 4. Hassanein T, Blei AT, Perry W, et al. *Am J Gastroenterol.* 2009;104(6):1392-1400. 5. Bass NM, Mullen KD, Sanyal A, et al. *N Engl J Med.* 2010;362(12):1071-1081.

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