

Economic Burden of Overt Hepatic Encephalopathy and Pharmacoeconomic Impact of Rifaximin

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INTRODUCTION

- Hepatic encephalopathy (HE) is a common neurologic cirrhosis-related complication and is associated with a substantial economic burden¹⁻³
 - HE-related cognitive impairment ranges from minimal (covert) HE, which requires detection using specialized testing, to overt HE, which is characterized by clinically identifiable symptoms (eg, confusion, personality and behavioral changes, lethargy)¹
 - Patients with a history of overt HE are at an increased risk for recurrence: 1 study reported a 23% increase in the risk of HE recurrence with each additional overt HE episode experienced (hazard ratio, 1.23; 95% confidence interval [CI], 1.19–1.29)⁴
- Management of overt HE includes treatment of acute HE episodes and reducing the risk of HE recurrence¹
 - Rifaximin^{*} has been shown to reduce the risk of overt HE-related hospitalization in adults with a history of overt HE⁵⁻⁷
 - Practice guidelines recommended lactulose as first-line therapy for acute HE episodes, while lactulose combined with the nonsystemic antibiotic rifaximin is recommended for reducing the risk of overt HE recurrence¹

AIM

- To provide an overview of direct HE-related costs and potential benefits of rifaximin in reducing HE-related hospitalization costs

METHODS

- A systematic review of PubMed and relevant congress abstracts (January 1, 2007, through June 23, 2017) was performed to identify publications reporting economic data related to HE and rifaximin and/or lactulose
- Published data were used to estimate the potential cost avoidance of HE-related hospitalizations with rifaximin^{5,8}
 - Incremental costs of therapy were not factored into this cost avoidance calculation

RESULTS

- Based on findings of the 16 reports identified for inclusion in the systematic analysis, mean HE-related direct annual costs ranged between \$5370 and \$50,120 per patient (Table 1)^{2,3,8-14}
- Worldwide, the mean duration of HE-related hospitalizations ranged between 5.9 days (United States)⁹ and 9.1 days (Thailand)¹⁰
 - In one US study, patients experienced a mean 2.4 HE-related hospitalizations in 2012⁹

RESULTS

Table 1. Economic Costs Associated With HE

Study (Perspective)	Country and Population	Costs*		
		Hospitalization	Non-Hospitalization	Total
Irish et al ⁹ (payer)	United States Pts with HE-related hospitalization (2012) Medicare claims database (n=1113)	Mean: \$25,364–\$58,625	—	—
	Thailand Pts with cirrhosis-related hospitalization (2010; n=92,301 admissions)	Mean: USD \$1394 ± \$2219	—	—
Roggeri et al ¹¹ (payer)	Italy Pts with ≥1 overt HE-related hospitalization during 2011 (n=381)	Mean direct costs per overt HE recurrence-related hospitalization: USD \$3838 ± \$1469	Mean annual drug cost: With recurrence: USD \$1865 ± \$2064 No recurrence: USD \$1340 ± \$1892	Annual costs: Pts with recurrence (n=124): USD \$24,293 Pts without recurrence (n=172): USD \$13,616 P<0.001
		Mean annual cost: With recurrence: USD \$24,293 ± \$20,084 No recurrence: USD \$13,816 ± \$26,488	Mean annual diagnostic and therapeutic procedure costs: With recurrence: USD \$764 ± \$1112 No recurrence: USD \$833 ± \$1735	
Benkovic et al ¹² (payer)	Croatia Pts with malnutrition and HE (2012; n=945)	—	Mean healthcare costs/pt: €1344	Total healthcare costs: €1,019,994
Lee et al ¹³ (payer)	China Pts with HE associated with benzodiazepine use enrolled in clinical studies (2005–2012) at single hospital (n=322)	Mean: USD \$231 ± \$14	Mean: Outpatient visits: USD \$27 ± \$3 ER visits: USD \$138 ± \$21	Overall medical costs: USD \$396 ± \$7
Andersen et al ¹⁴ (provider)	Denmark Pts with cirrhosis with previous HE-related hospitalization receiving outpatient rehabilitation (2009; n=19) vs pts not receiving rehabilitation (2008; n=14)	Median (range) costs for rehospitalization: Rehabilitation group: USD \$15,633 (\$0–\$75,535)	—	—
		No rehabilitation group: USD \$15,571 (\$0–\$87,004)		
El Khoury et al ⁹ (payer and/or provider)	Brazil, Canada, Asia-Pacific region, and Europe (systematic review; 11 studies; 1990–2011) Pts with HE related to HCV infection	—	—	Mean (range) global HE-related costs (2010 USD): \$13,270 (\$5370–\$50,120)
El Khoury et al ⁹ (provider)	United States (systematic review; 5 studies; 1997–2007) Pts with HE associated with hepatitis C virus infection	—	—	Mean HE-related costs (2010 USD): Year 1: \$16,430 Year 2: \$3810
Stepanova et al ⁹ (payer)	United States Pts with HE-related hospitalizations between 2005 and 2009 (n=111,090)	Mean charges: 2005: \$46,663 ± \$2180 2009: \$63,107 ± \$3244	Mean HE-related costs per pt: 2005: \$16,512 ± \$709 2009: \$17,812 ± \$764	Total HE-related hospitalization charges: 2005: \$4.677 billion 2009: \$7.254 billion

*Mean data include standard deviation. ER = emergency room; HCV = hepatitis C infection; HE = hepatic encephalopathy; pt = patient; SD = standard deviation; USD = US dollars.

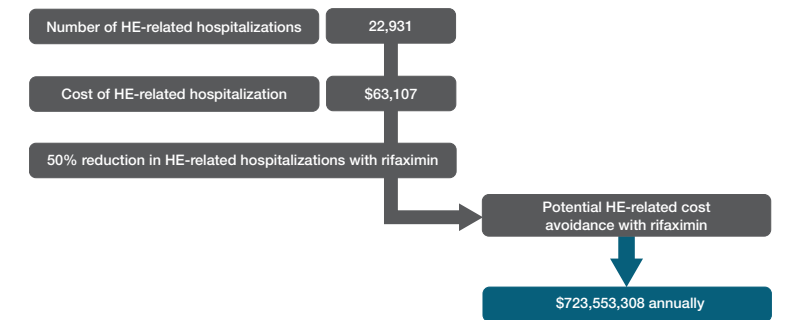
- Treatment with rifaximin plus lactulose was associated with a decrease in hospitalizations^{15,16} and reduced healthcare costs (Table 2)¹⁷⁻²³
- Data suggest that rifaximin in combination with lactulose may be cost effective versus lactulose alone for patients with a history of overt HE
- In one US study, rifaximin significantly reduced the odds of rehospitalization within 30 days for patients with overt HE (adjusted odds ratio, 0.39; 95% CI, 0.16–0.87; P=0.02)²⁴
- Potential overt HE-related cost avoidance attributed to decreased hospitalizations with rifaximin plus lactulose in the United States were estimated at >\$723 million annually (2009 charges; Figure)^{5,8}

Table 2. Pharmacoeconomic Profile of Rifaximin

Country, Patient Characteristics, and Endpoint(s)*	Outcomes
United States ²³ Recurrent overt HE Costs (drug costs, hospitalizations, liver transplant)	Rifaximin + lactulose vs lactulose • Life expectancy ↑ with rifaximin + lactulose vs lactulose (lifetime, 5.7 y vs 2.8 y) • Liver transplant opportunity ↑ 2-fold with rifaximin + lactulose vs lactulose • Hospitalizations ↓ with rifaximin + lactulose vs lactulose during 6 mo (0.27/pt vs 0.51/pt)
Outcomes (hospitalizations, LY, QALY)	These outcomes estimated at additional lifetime cost of rifaximin: \$59,777 per pt; resulting in: \$20,287/LY for rifaximin + lactulose vs lactulose vs \$26,672/QALY for rifaximin + lactulose vs lactulose
Belgium ¹⁸ Recurrent overt HE ICER, derived from QALY [†] (2010 costs)	Lactulose (SOC) • Average cost: €44,190 • 1.9 QALY/pt Rifaximin + lactulose • Average cost effectiveness: €23,258/QALY ICER • Average cost: €31,262 • 2.5 QALY/pt • Average cost effectiveness: €12,505/QALY • €21,547/QALY for rifaximin + lactulose vs lactulose
France ¹⁹ History of overt HE (≥2 episodes); currently in remission ICER, derived from QALY [†]	Lactulose (SOC) • Average cost: €5503 • 0.967 QALY/pt Rifaximin + lactulose • Average cost: €14,411 • 2.094 QALY/pt ICER • €19,187/QALY for rifaximin + lactulose vs lactulose • €18,517/QALY for rifaximin + lactulose vs lactulose
Netherlands ²⁰ Recurrent overt HE ICER, derived from QALY [†] (2010 costs)	Lactulose (SOC) • Average cost: €82,968; 1.89 QALY/pt Rifaximin + lactulose • Average cost: €88,386; 2.45 QALY/pt ICER (5 y) • €9576/QALY for rifaximin + lactulose vs lactulose
Sweden ²¹ Recurrent overt HE ICER, derived from QALY [†] (2012 costs)	Lactulose (SOC) • Average cost: €42,522; 1.83 QALY/pt Rifaximin + lactulose • Average cost: €32,667; 2.38 QALY/pt ICER (5 y) • €17,918/QALY for rifaximin + lactulose vs lactulose
United Kingdom ¹⁷ Overt HE [‡] Cost effectiveness of rifaximin (2013/2014 costs)	1 y before vs 1 y after rifaximin • Mean annual emergency inpatient admission costs: £12,522 vs £5915, respectively Lactulose (SOC) • Average cost: £23,545; 1.83 QALY/pt Rifaximin + lactulose • Average cost: £23,545; 1.83 QALY/pt ICER • 5 y: £1083/QALY for rifaximin + lactulose vs lactulose • 10 y: £4470/QALY for rifaximin + lactulose vs lactulose • Lifetime: £7215/QALY for rifaximin + lactulose vs lactulose
United Kingdom ²² Recurrent overt HE ICER, derived from QALY [†] (2012 costs)	Lactulose (SOC) • Average cost: £23,545; 1.83 QALY/pt Rifaximin + lactulose • Average cost: £23,545; 1.83 QALY/pt ICER • 5 y: £1083/QALY for rifaximin + lactulose vs lactulose • 10 y: £4470/QALY for rifaximin + lactulose vs lactulose • Lifetime: £7215/QALY for rifaximin + lactulose vs lactulose

*Historically, a 1 € converted annual average was 1.4 to 1.1 USD during 2010–2016 and 1 € converted annual average was 1.6 USD during 2012–2014.
†Markov state transition model.
‡In this study, costs were compared before and after initiation of rifaximin treatment.
HE = hepatic encephalopathy; ICER = incremental cost-effectiveness ratio; LY = life-years; QALY = quality-adjusted life years; SOC = standard of care.

Figure. Potential US Annual HE-Related Cost Avoidance With Rifaximin (2009 US Charges)^{5,8}



HE = hepatic encephalopathy.

CONCLUSIONS

- Economic data are favorable for the use of rifaximin in reducing the risk of overt HE-related hospital admissions in adults with cirrhosis
- Rifaximin administration should be considered at discharge in adults with cirrhosis hospitalized due to overt HE to reduce the risk of rehospitalization

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*Rifaximin is indicated in the United States for reducing the risk of overt hepatic encephalopathy recurrence in adults.

