Hepatic Encephalopathy: A Paradigm Shift

Dieter Häussinger

The most recent understanding of the pathogenesis of hepatic encephalopathy (HE) is that heterogeneous precipitating factors cause a low-grade cerebral oedema and an oxidative stress response with formation of reactive oxygen and reactive nitrogen species (ROS/RNS). This triggers multiple changes in signalling pathways and causes protein and RNA modifications, which result in alterations in gene expression and neurotransmission. These events in turn alter synaptic plasticity and lead to disturbances of oscillatory networks in the brain that are responsible for the cognitive and motoric symptoms of HE (Figure 1).\(^1\)\(^2\)\(^3\) This pathophysiological series of responses has been demonstrated in both, the human brain and in animal experiments.

Gene expression in the human cerebral cortex controls individuals with liver cirrhosis with and without HE. As shown by whole genome gene expression analysis, 434 genes are specifically upregulated in HE in the brain (Figure 2). Upregulation of these genes are specific for HE and cannot be detected in cirrhotic patients without HE.\(^4\)

This new pathophysiological concept is not the only paradigm shift; there are new diagnostic methods, new aspects of sociomedical relevance and new treatment options available to treat HE.
HE Epidemiology

Peter Jepsen

The International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) issued a consensus statement (2011)\(^5\) emphasising that hepatic encephalopathy (HE) is a continuum of worsening cognitive function. However, in clinical practice HE is defined by clinically relevant categories; patients who are unimpaired, patients with covert HE and patients with overt HE. The transition from unimpaired to covert HE is defined by the results of specialised tests and the transition from covert to overt HE is defined by flapping (asterixis). The specialised tests used to diagnose covert HE is a huge research topic in its own right and is not discussed here.

Although surprisingly few studies have examined how HE affects life expectancy, it is evident that overt HE is associated with a short survival time. Bustamente et al. (1999)\(^6\) reviewed 111 patients with overt HE and found an expected residual survival time of approximately 6 months. In a landmark study of patients with alcoholic cirrhosis, Saunders et al. (1981)\(^7\) compared the impact of various cirrhosis complications and also found that HE was associated with a survival time of approximately 6 months. More recently a Danish study\(^8\) of alcoholic cirrhosis patients found that with the improvements in the management of variceal bleeding, HE was clearly the most lethal cirrhosis complication and has the greatest impact on patient mortality (Figure 3).

Covert HE is not associated with the steep short-term mortality seen with overt HE. This was shown in a study\(^9\) of 271 cirrhosis patients with mixed aetiology, a significant difference in survival between patients with overt HE and patients with covert HE was observed. These results confirm what would be expected because covert HE is an earlier manifestation of the spectrum of neurocognitive impairment in cirrhosis.

HE affects not only mortality but quality of life (QoL). QoL was compared in 544 cirrhosis patients with or without HE in the largest QoL study to date.\(^10\) The patients included in the study were not suffering from the most severe forms of HE because they had to have the ability to fill out a questionnaire. The Nottingham Health Profile and the SF-36, both of which are generic measures of health-related QoL, were used to assess the effects of HE on the physical and mental domains of the patients. The 2 groups of patients with cirrhosis, those with HE and those without HE, were compared with a baseline population sample. The results showed that cirrhosis with or without HE does not cause pain. However, cirrhosis, and to an even greater extent HE, affects the physical domains of the patient. The Nottingham Health Profile showed that energy, mobility and sleep were significantly affected in patients with HE and the SF-36 indicated that physical function was affected. Overall, the results showed that the physical domains were more affected by HE than the mental domains. However, this is possibly due to HE patients’ poor insight into their own mental capacity.

It is less clear whether covert HE affects QoL. Studies have shown conflicting evidence; with the milder forms of HE it is difficult to disentangle the effects of cirrhosis on QoL from covert HE.\(^10\) In addition, the differences in cirrhosis severity, aetiology and the diagnostic criteria make it difficult to compare studies. However, it is clear that covert HE does cause problems with attention, visuospatial abilities and psychomotor speed, for example patients with
covert HE have difficulties in completing complicated work tasks and driving a car.

HE imposes a burden on the caregivers of cirrhosis patients. Montagnese et al.\(^{11}\) measured the caregiver burden in 31 caregivers (94% were relatives). The caregivers completed a questionnaire (The Caregiver Burden Inventory) that focused on the time devoted to care for the patient and the psychological, physical, social and emotional burden they experienced. The results showed that the burden on the caregiver was markedly greater for caregivers to patients with overt HE than for caregivers to cirrhosis patients without HE. The study concluded that in HE patients there is a burden on both the caregivers and the patients themselves.

Overt HE is a relatively uncommon presentation at the time of cirrhosis diagnosis. In a study\(^{12}\) of 1,115 cirrhosis patients only 10% of the study population were reported to have overt HE when cirrhosis was diagnosed. Similarly, this prevalence was shown in a study of 250 patients with alcoholic cirrhosis,\(^7\) 10% had overt HE at the time of cirrhosis diagnosis. A further study\(^8\) of 466 Danish patients showed that 11% had overt HE at the time of cirrhosis diagnosis. The results of these studies indicate that in the majority of patients, there is time to intervene and prevent the development of HE.

The presence of covert HE is much less clearly defined. Several studies have found that the prevalence of covert HE in cirrhosis patients is 25% to 50%, although some have reported a prevalence as high as 75%; the difference seen in the results are due to the variance of the study population and diagnostic criteria.\(^{13-15}\) Covert HE is a warning sign that overt HE may ensue. This was shown in a Dutch study\(^{16}\) of 116 cirrhosis patients with mixed aetiology. Twenty-five patients had covert HE, and in 2.5 years of follow-up 56% of these patients developed overt HE.

Patients who have already developed cirrhosis complications are much more likely to develop HE. The risk of a first episode of overt HE was compared between patients who had not developed cirrhosis complications and patients who had already had variceal bleeding or ascites. Those who had not developed complications had a 5 year risk of a first episode of overt HE of 7% compared with 26% in those with other complications (Figure 4). These findings are consistent with the observations that overt HE is a rare first complication of cirrhosis.\(^6\)

In studies of patients with viral cirrhosis, a recent
Cuban study\textsuperscript{17} examined the risk of overt HE in 402 patients with compensated hepatitis C virus (HCV) cirrhosis. Those without varices had a 5-year risk of overt HE of approximately 5% compared with 15% in those who had non-bleeding varices. These findings are consistent with an Italian study that reported a 5-year risk of overt HE of 9% and a 10 year risk of 25%\textsuperscript{18} in compensated cirrhosis. Conversely a further study\textsuperscript{19} found a much lower risk of overt HE, approximately 5% after 10 years. This lower risk may be explained by the differences in diagnostic criteria for overt HE.

The vaptan trials were conducted to examine whether patients with ascites might benefit from satavaptan treatment. The 3 trials included a total of 1,198 cirrhosis patients with ascites, 25% of whom had previously had an HE episode. Data from the 1-year follow-up period showed that 27% of the patients had at least one episode of overt HE.\textsuperscript{20}

The different risk estimates shown in the various studies is probably due to the differences in the prevalence of other risk factors for developing HE. The risk factors for developing HE are usually divided into precipitants and more remote risk factors. Precipitants are those risk factors that manifest immediately before overt HE occurs, including constipation, dehydration, infections, variceal bleeding and medications. These produce inflammation or an increase in nitrogen load. The more remote risk factors for developing overt HE include previous episodes of overt HE, covert HE, ascites, and hyponatraemia. In addition, Jepsen et al. (2012)\textsuperscript{21} found that poor galactose elimination capacity (GEC, a measure of hepatic metabolic function) is a strong risk factor for overt HE but is not a risk factor for ascites or variceal bleeding. The role of other risk factors in the development of HE such as cirrhosis aetiology and comorbidity remain largely unknown.

In summary, HE is a continuum; in its overt form it is associated with a very high mortality with an expected survival time of approximately 6 months. The covert form of HE is an early warning sign of overt HE, however covert HE causes its own specific problems. HE affects QoL and is a burden on caregivers as well as on the patients themselves. The prevalence of HE at the time of cirrhosis diagnosis is 10% however, the risk of development is highly variable ranging from approximately 5% to more than 25% after 5 years.

### Strategies to Improve the Diagnosis and Management of Hepatic Encephalopathy

**Rajiv Jalan**

The changing paradigm of hepatic encephalopathy (HE) illustrates the current problems in the management of the syndrome. This includes the interaction between ammonia and inflammation and how new concepts of acute and chronic liver failure will impact on how HE is understood and treated in the future.

Two factors lead to the development of the syndrome, liver disease and progression (which is linked with liver injury and maybe limited or on-going), and coincidently increased bacterial translocation as a result of a number of interacting factors. It is thought that these two factors lead to the development of the complex progression of hepatic fibrosis. This leads to compensated cirrhosis or decompensated cirrhosis. Decompensated cirrhosis is typically associated with the syndrome of hepatic encephalopathy.

Whether there is fibrotic liver disease, compensated cirrhosis or decompensated cirrhosis the issue is complicated by the effect of the ‘second hit’. A ‘second hit’ implies the effect of a superimposed hepatic event such as exacerbation of liver disease with drugs, viruses or toxins, or an extrahepatic event such as infection, trauma, variceal bleeding, insertion of a transjugular intrahepatic shunt or surgery. This can lead to the development of HE which is a precipitated syndrome. Cirrhotic patients depict altered host response to injury, which is associated with multiple organ dysfunction, and a resulting...
syndrome that is referred to as acute or chronic liver failure. HE is one of the characteristic complications.

Peter Ferenci (1998) defined the types of HE: Type A associated with acute liver failure; Type B associated with portal systemic bypass, no intrinsic hepatocellular disease; Type C associated with liver cirrhosis and portal hypertension/or portal-systemic shunts. This definition remains a useful tool for discerning the types of HE and classifying patients.

Overt HE is just the tip of the iceberg. A larger proportion of patients lie in the domain of unrecognised syndrome referred to as minimal hepatic encephalopathy. Pre-minimal HE is being increasingly recognised as a sub-group of patients who have normal neuropsychological test results but have an increased number of associated symptoms such as fatigue, undue anxiety, autonomic dysfunction and depression. This area of HE is where understanding needs to be increased and therefore, where the changing paradigm of the perception and treatment of HE is predicted.

Patients with minimal HE (MHE) have a poor quality of life (QoL), they are tired, lack concentration and some cannot drive. It is in this patient group that differences can be made and new treatments developed. If patients with MHE develop infection or bleeding complicates the syndrome and can lead to the overt form of HE.

An analysis of 1,400 patients identified the features of patients with HE in acute on chronic liver failure. The analysis defined one group of patients that had no other attendant organ dysfunction i.e. no acute-on-chronic liver failure (ACLF), and showed that in this group mortality rates were very low (4%). In contrast, the analysis found that if a patient had associated organ dysfunction identified by high bilirubin, high creatinine, low sodium and a marked inflammatory response, a precipitating event and a higher Model End Stage Liver Disease (MELD) there is an increased risk of mortality (30%). These results show that patients with associated organ dysfunction are likely to have a higher mortality; however this mortality is not necessarily dependent on the severity of HE but on the ancillary features. This is a paradigm shift in the understanding of overt HE identifying possibly two or more sub-classes of patients. Therefore reclassification of the features of HE will be necessary in the future.

At present, HE is graded using the West Haven Criteria for semi-quantitative grading of mental state; from Grade 1 to Grade 4. The diagnosis and categorisation of patients with Grades 2, 3 and 4 is straightforward; the problem is diagnosing Grade 1 HE. This is because there is a variety of symptomatology that is difficult to define. Grade 1 HE is defined as trivial lack of awareness, euphoria, anxiety, shortness of attention span and impaired performance but these symptoms could be applied to most people in particular sets of circumstances who do not have HE! It is essential that sub-classifications of this early form of HE are developed to enable clear definition and clear diagnosis of the syndrome.

In the pathophysiology of HE, low grade cerebral oedema is very important. The cell that is swollen is the astrocyte. Astrocytes are located very close to the blood vessels in the brain and form part of the blood-brain barrier. In severe acute liver failure, the astrocytes become very swollen. It is thought that this swelling is due to ammonia, although cerebral inflammation can also cause the astrocytes to swell. High levels of ammonia can be seen in different categories of HE patients but whether the levels correlate with outcomes is unknown. Ammonia causes cells in the brain to swell; it is thought that this is caused by the accumulation of the metabolite glutamine allowing attraction of water into the cell which in turn leads to cell swelling. In the last 15 years it has become apparent that the role of ammonia in this process is complex. Ammonia is produced in the gut, not necessarily by the action of bacteria, but by the uptake of glutamine into the gut, the metabolic generation of ammonia is one of the future targets of therapy. The role of the kidney is very important both in ammoniagenesis and ammonia excretion. millimolar quantities of ammonia are excreted in the urine every day providing a huge opportunity to impact on ammonia concentrations.

The classical understanding of the pathogenesis of HE is that liver failure results in increased ammonia which causes brain oedema. However, the alteration of bioenergetics should be considered, whether the alteration of bioenergetics is pathophysiologically important or is a consequence of increased ammonia is unknown. The alteration of bioenergetics interacts significantly with the whole systemic inflammatory response which may act both inside and outside the brain through the blood brain barrier. This leads to the increased activity and/or expression of transcription factors which may lead to brain oedema and consequently neurological dysfunction.

Clinical data confirms that ammonia is synergistic with inflammation in the pathogenesis of HE. Gut permeability and its modulation is an important
factor in the inflammatory response, endotoxemia is thought to prime the circulation in the brain by upregulation of the Toll-like receptor 4. This increases permeability, alters liver function, primes the circulation, organs, kidneys and brain resulting in the predisposition to the effect of the 'second hit'. The outcome of this process is HE.

The importance of targeting the gut is highlighted by the significant difference seen in the development of HE following an acute variceal bleed between patients who are treated early with lactulose compared with those who are untreated. This suggests that the occurrence of the overt form of HE can be prevented. Therefore, the prevention of overt HE is a major treatment goal.

Treatment of patients with large portosystemic shunts is very difficult to manage. Riggio et al (2005) compared patients who did not have HE and were having transjugular-intrahepatic-portosystemic-shunts (TIPS) inserted. Seventy-five patients were randomised to 3 arms; lactitol, rifaximin or no treatment. The results showed that there was no difference in patient outcome with any of the treatments used as prophylaxis to prevent HE following TIPS. Therefore, the role of shunting in the development of these syndromes is important. However, rifaximin treatment has illustrated the principle that modulating the gut can lead to a reduction in the recurrence of HE.

In patients who don’t respond to treatment, albumin dialysis may be useful. Albumin is being used as an adsorbent; it was thought that this molecule is a volume expander but it is actually a very important antioxidant and has a lot of other functions and is critically involved in the process of binding toxins and removing endotoxins. Seventy patients who had failed all forms of treatment in intensive care were studied, and extracorporeal albumin dialysis led to a significantly greater wake up rate in patients treated with this device and the coma time was reduced. Although no difference in survival with the treatment was seen, the study showed that if the patient responded to therapy and the HE improved, the patients were more likely to survive.

The treatment algorithm for overt HE (Figure 5), includes the following steps; confirmation of the cause and other possible causes ruled out. If HE is confirmed the precipitating factor should be found and treated. If the precipitating factor is not found the patient should be treated with lactulose (lactulose appears to be the best treatment at the present time) and albumin dialysis considered.

In conclusion, ammonia and inflammation are synergistic, but may be independent of each other, in the development of the syndrome of HE, providing 2 important targets for therapy. Current approaches for HE are improving. Lactulose is the main treatment for MHE and for the primary prophylaxis of bleeding.
Rifaximin is used for secondary prophylaxis, and in severe acute HE, albumin dialysis is usefully. In the future, there will be several more drugs available to treat HE initiating a paradigm shift that will enable improved classification of patients. There is no strategy that has been shown to reduce ammonia consistently in cirrhosis; however two new agents show promise (HPN-100 and ornithine phenylacetate). There will be more development in this area in the future.

**Prevention of Recurrence of Overt Hepatic Encephalopathy**

Fred Poordad

The algorithm for the management of a patient with possible overt hepatic encephalopathy (HE) involves confirming the HE and then searching for precipitating factors. However, in patients with progressive recurrent HE approximately 80% of the time a clear precipitating factor is not found. If precipitating factors are identified, treatment should be directed at these (this does not always involve long term therapy). When precipitating factors are not found the patient should be treated by admission to intensive care (HE grade 3 or above) and specific therapy for the underlying cause as well as HE therapy with lactulose or rifaximin commenced.

There are various management options for patients with recurrent overt HE these include non-absorbable disaccharides (lactulose and lactitol) and non-absorbable antibiotics (rifaximin and neomycin). Rifaximin and neomycin are both FDA approved, though only neomycin is approved for the treatment of acute HE. Other therapies such as sodium benzoate are not currently licensed in the EU to treat HE.

The rationale for the use of non-absorbable disaccharides is to lower ammonia by metabolic trapping. Non-absorbable disaccharides are thought to work by protonating ammonia to ammonium and enhancing the excretion of the compound, however there are other mechanisms involved such the inhibition of bacterial ammonia production and the purgatory effect of non-absorbable disaccharides which remove bacteria from the colon. Yet studies using lactulose or lactitol do not show this to be an effective treatment over placebo in HE. Conversely in clinical practice, even though no effect on mortality has ever been shown, these treatments do appear to be effective, but it is difficult to show this in clinical trial settings. The most challenging aspect of treating patients with non-absorbable disaccharides is that they can cause a tremendous number of adverse events (AEs), which include abdominal bloating, gas/flatulence, unpredictable diarrhoea and, if used to extremes, can lead to volume contraction and electrolyte abnormalities. These AEs are distressing for the patient, often to the point of the patient becoming non-adherent to therapy. Bajaj et al (2010) showed that patients with HE treated with lactulose typically experienced a recurrence within 9 months. 3 out of 4 of these patients required hospital admission, and 39% of those admitted to being non-compliant to lactulose treatment. In addition, 8% of the patients experienced lactulose-associated dehydration. The multivariate analysis predictors of recurrence showed the 2 variables that predicted readmission and recurrence of HE were non-adherence to lactulose treatment (OR, 3.26) and a high Model for End-stage Liver Disease (MELD) score (OR, 1.14).

Sodium benzoate increases ammonia metabolism and renal elimination. It is not FDA or EU approved for the treatment of HE. Limited clinical studies exist regarding the use of sodium benzoate in the treatment of HE, and one study examining basal/post glutamine challenge ammonia levels in cirrhotic patients suggested a note of caution in its use. Unsurprisingly sodium benzoate has not been widely adopted as a treatment for HE. Non-absorbable antibiotics are thought to reduce the production of gut-derived ammonia by decreasing the bacteria that produce it. However, it has become apparent that there are other mechanisms involved suggesting that the complete mechanism is not fully understood. There are few clinical studies that assess this mechanism in relation to neomycin treatment for HE. Neomycin is absorbed at a rate of up to 5%, therefore it is not truly a non-absorbed antibiotic. In addition, the use of neomycin is limited due to its ability to cause hearing loss and it has the potential to cause nephrotoxicity, particularly in patients with high MELD scores. Consequently, neomycin is not a recommended choice for the treatment of HE.

The efficacy and safety of rifaximin (Xifaxan) in HE has been studied extensively both in the EU and the US. The trials include a double-blind, randomised, dose-finding multi-centre study, open-label studies, several comparative randomised controlled trials against neomycin, paromomycin, lactulose and lactitol, and one multi-national placebo-controlled trial. A review of randomised trials that compared non-absorbable disaccharides with antibiotics and placebo...
showed that overall antibiotics produced a positive effect in the management of HE and were superior to non-absorbable disaccharides in improving HE. This indicates that although disaccharide treatment is a well-established treatment, and often the first-line treatment for HE, (possibly due to its relatively low cost), the efficacy of these compounds need to be assessed.

The treatment options for HE have distinct advantages and disadvantages. Treatment efficacy estimates in patients with overt HE based on pooled data (generated primarily for pharmacoeconomic evaluation) showed varying clinically significant improvements in patients treated with lactulose, lactitol, neomycin and rifaximin of 68%, 69%, 64% and 90%, respectively. Though these were not head-to-head comparisons in the same trial, the estimates provide relative differences in an overview of the efficacy of the different treatments.

Following recovery from overt HE the goal is to maintain the patient in remission. It must be accepted that it is not a curable disease and that a further episode is likely, therefore the aim is to delay the next episode of HE for as long as possible. Historically, lactulose has been the standard treatment (possibly due to a lower medication cost per patient). However, rifaximin appears to have a superior tolerability and efficacy profile. In addition, early data suggests that preventing hospital admission could decrease morbidity associated with in-patients and decrease overall healthcare costs.

A Phase III randomised, double-blind, placebo-controlled trial evaluated rifaximin for the maintenance of HE remission. The inclusion criteria were that patients had experienced at least 2 episodes of West Haven Grade 2 or higher HE in the 6 months prior to enrolment, and at the time of enrolment were in remission (Grade 1 or Grade 0 disease). The patients were randomised to receive rifaximin or placebo over a 6-month period; due to their previous HE episodes, 90% of the patients were taking concomitant lactulose. It was deemed unethical to remove lactulose and randomise the patients to placebo alone; therefore the background treatment for the majority of the patients was lactulose. The primary endpoint of the study was the first HE breakthrough. The results showed no HE breakthrough in 77.9% of patients receiving rifaximin versus 54.1% of patients receiving placebo (HR: 0.42; P=0.0001), 86.4% of patients receiving rifaximin did not require hospitalisation for an episode of HE compared with 77.4% receiving placebo (HR: 0.50; P=0.01) during the 6 month study period. No significant differences in drug-related adverse events (AEs) were seen between the 2 groups and no novel emergent AEs were seen (Table 1).

Quality of life (QoL) was assessed in HE patients treated with rifaximin compared with placebo in a pivotal Phase III trial. The patients were administered the Chronic Liver Disease Questionnaire (CLDQ) at baseline and every 4 weeks until the end of treatment. The CLDQ is a disease specific instrument to assess health-related QoL; it incorporates 29 items across 6 domains and a 7-point scale with higher scores indicating improved QoL. The area under the curve for CLDQ was normalised by exposure time to calculate the time-weighted average. The mean time-weighted average for overall QoL (P=0.0093) and all 6 subdomains in the rifaximin arm were significantly greater compared with the placebo arm. The results indicated an improvement in QoL in patients that were treated with rifaximin (Figure 6).

Breakthrough HE can be prevented with 6 months treatment of rifaximin in 1 out of 4 cases, and 1 out of 9 cases of hospitalisation-related HE can be avoided. This was demonstrated in a single centre

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Xifaxan® 550mg b.i.d. (n=140) n (%)</th>
<th>Placebo (n=159) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>112 (80.0)</td>
<td>127 (79.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (14.3)</td>
<td>21 (13.2)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>21 (15.0)</td>
<td>13 (8.2)</td>
</tr>
<tr>
<td>Ascites</td>
<td>16 (11.4)</td>
<td>15 (9.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (12.1)</td>
<td>18 (11.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15 (10.7)</td>
<td>21 (13.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18 (12.9)</td>
<td>13 (8.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (10.0)</td>
<td>17 (10.7)</td>
</tr>
</tbody>
</table>

Table 1. Rifaximin (Xifaxan®) in HE: rate of adverse events.
study comparing rifaximin and lactulose in the management of HE. The average length of hospital stay for the lactulose group was 5.0 days compared with 3.5 days in the rifaximin group (P<0.001). The total annual cost of hospitalisation for the lactulose group was $413,285 compared with $7,958 in the rifaximin group, showing a significant cost differential of $5,327.

Rifaximin is a semisynthetic antibiotic that is a derivative of rifamycin. It has broad coverage against gram-positive and gram-negative bacteria, aerobes and anaerobes. Rifaximin is a non-systemic antimicrobial with absorption of less than 0.4%, it is concentrated in the gastrointestinal tract and excreted in the faeces and has a very low propensity to produce clinically meaningful resistance. Dose finding studies have shown that 1000mg is the appropriate dose per day for the treatment of HE and multiple doses of rifaximin do not result in accumulation. In addition, no clinically relevant drug interactions have been observed.

In conclusion, there are limited therapeutic options for HE, most of the historical therapies have multiple side effects. There is now a broad spectrum, non-absorbed antibiotic therapy, rifaximin (Xifaxan™) that is well tolerated, effective and is suitable for long term use.

Future research for new therapeutic options will focus on enhancing survival in advanced liver disease.

**Figure 6. Chronic Liver Disease Questionnaire results with rifaximin treatment in HE.**
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