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Emergent Management of Hepatic Encephalopathy: An Updated Review

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Abstract:

Background: Hepatic encephalopathy (HE) is a neuropsychiatric disorder associated with liver dysfunction. It presents as overt or minimal HE and significantly impacts prognosis, particularly in cirrhosis and acute liver failure. Despite advancements, HE remains a clinical challenge due to its heterogeneity and the complexities in diagnosis and management.

Aim: To review and summarize the emergent strategies for diagnosing and managing HE, including clinical, pharmacological, and innovative therapeutic approaches.

Methods: A comprehensive analysis of current literature was conducted, emphasizing standardized classification systems, diagnostic modalities, and management protocols. Key areas include addressing precipitating factors, employing pharmacological treatments, and exploring emerging therapies like fecal microbiota transplantation (FMT).

Results: Standardized criteria, including the West Haven classification, aid in grading HE severity. Clinical and neuropsychological assessments remain pivotal, complemented by imaging and laboratory tests. Effective management involves treating precipitating factors such as infections, gastrointestinal bleeding, and electrolyte imbalances. Pharmacological options include lactulose, rifaximin, and l-ornithine l-aspartate, which target ammonia detoxification. Emerging therapies like FMT show promise in improving cognitive outcomes by restoring gut microbiota diversity. Liver transplantation remains critical for long-term survival in advanced cases.

Conclusion: HE management necessitates a multidisciplinary approach, integrating established and innovative interventions. Addressing precipitating factors, optimizing pharmacological regimens, and exploring novel therapies are essential for improving outcomes. Future research should validate emerging therapies to integrate them into clinical practice effectively.

Keywords: Hepatic encephalopathy, liver dysfunction, ammonia detoxification, gut microbiota, fecal microbiota transplantation, liver transplantation.

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Introduction:

Hepatic encephalopathy (HE) encompasses a spectrum of neuropsychiatric disorders observed in patients with liver dysfunction, provided that other underlying brain conditions are excluded. It represents a significant clinical challenge, particularly in individuals with cirrhosis, and is a defining factor in the prognosis of acute liver failure. HE is categorized into two forms: overt HE and minimal (covert) HE. Overt HE is diagnosed based on observable symptoms and clinical findings, while minimal HE often necessitates psychometric or neurophysiological testing. However, minimal HE can sometimes be inferred from a detailed history provided by the patient or their caregivers. In acute liver failure, substantial brain swelling may occur, with elevated intracranial pressure complicating approximately 25% of cases involving acute or hyperacute liver failure and 9% of subacute liver failure. In the context of cirrhosis, HE manifests as a wide range of neuropsychiatric disturbances, from severe states such as stupor and coma to subtle impairments in higher cognitive functions that are detectable only through psychometric evaluations. The annual incidence of overt HE in cirrhotic patients is estimated to be 20%, and 60–80% of these patients exhibit evidence of minimal HE on testing.

Definitions and Classification

The heterogeneous clinical presentation of HE has posed challenges in comparative research, necessitating the adoption of standardized terminology for classification. HE is classified into three types: Type A (associated with acute or hyperacute liver failure), Type B (occurring due to portosystemic bypass without intrinsic liver disease), and Type C (linked to cirrhosis and portal hypertension with portosystemic shunting). Clinical presentations include acute encephalopathy due to liver dysfunction, recurrent or episodic mental status alterations in cirrhotic patients, persistent neurological deficits despite resolving liver injury, and minimal or covert encephalopathy detectable only through neuropsychological tests.

Clinical Staging

Staging overt HE remains complex due to its variable nature. The West Haven criteria provide a widely recognized framework for grading HE severity, ranging from Grade 0 (no clinical abnormalities) to Grade 4 (coma). In severe cases, the Glasgow Coma Scale is employed as an objective measure of impaired consciousness. For example, Grade 1 HE may involve symptoms like short-term memory loss and sleep–wake cycle disturbances with a Glasgow Coma Scale score of 15, while Grade 4 HE is characterized by unresponsiveness or coma, reflected in scores as low as 3–6.

Pathogenesis

In liver injury, impaired urea synthesis prompts the brain to serve as an alternative pathway for ammonia detoxification. Astrocytes play a crucial role by converting ammonia into glutamine; however, hyperammonaemia leads to glutamine accumulation within astrocytes, resulting in osmotic stress and cellular swelling. In acute liver failure, this process contributes to cytotoxic brain edema. Magnetic resonance imaging (MRI) has provided compelling evidence of increased brain water content in patients with minimal HE, which correlates with neuropsychological deficits and is reversible post-liver transplantation. Emerging evidence highlights the gut microbiome's critical role in HE pathogenesis. Dysbiosis in the salivary and gut microbiota, characterized by diminished bacterial diversity and the dominance of pathogenic species, increases gut permeability and fosters bacterial translocation, endotoxemia, and dysregulated immune responses. Infection serves as a common precipitant of HE, with studies showing a rapid progression in HE severity in acute liver failure patients experiencing heightened inflammation. These findings are consistent across individuals with cirrhosis [1].

Diagnosis

History and Clinical Examination

Diagnosing hepatic encephalopathy (HE) necessitates evidence of liver disease based on clinical history or examination findings. A comprehensive history and meticulous physical examination are crucial, as differential diagnoses include intracranial pathologies, electrolyte disturbances, and sepsis. During the

evaluation, it is imperative to identify any precipitating factors, such as gastrointestinal bleeding or infection. Symptoms such as a reversal of the sleep–wake cycle, impaired concentration, and short-term memory deficits may indicate minimal HE. Simultaneous evaluation and stabilization of the airway, along with monitoring vital parameters, are essential at the onset of assessment. Asterixis, characterized by a flapping tremor, should be differentiated from similar presentations in alcohol withdrawal or intoxication. Hyper-reflexia is another clinical feature, while the elicitation of focal neurological deficits necessitates consideration of alternative diagnoses. Clonus is commonly observed in patients with grade 3 or 4 HE [2, 3].

Investigations

Laboratory Tests

Initial diagnostic efforts should include routine blood biochemistry and glucose measurements. Investigations must focus on identifying precipitating factors such as infection, electrolyte imbalances, or gastrointestinal bleeding. If ascites is clinically apparent, a diagnostic paracentesis is mandatory to exclude spontaneous bacterial peritonitis, which is confirmed by an ascitic fluid polymorphonuclear leukocyte count of $\geq 250/mm^3$. A complete septic work-up, including urine and blood cultures, should also be conducted. Blood ammonia levels often correlate with HE severity, but elevated ammonia levels can also occur in individuals without overt HE or liver disease. Furthermore, ammonia levels may remain elevated after clinical HE resolution. However, a normal blood ammonia concentration has a negative predictive value and should prompt further evaluation of alternative causes for altered mental status in patients presenting with reduced consciousness or delirium [4].

Imaging

Computed tomography (CT) scans of the brain are commonly performed to exclude alternative causes of altered consciousness, particularly when the patient's history is limited. In cases of acute liver failure, CT imaging may reveal increased intracranial pressure; however, critically ill patients may not tolerate transport for imaging. For low-grade HE, CT findings are typically nondiagnostic, although imaging can be used to rule out intracranial hemorrhage in patients with coagulopathy or thrombocytopenia. Magnetic resonance imaging (MRI) of the brain serves as a valuable diagnostic modality by excluding differential diagnoses such as hippocampal atrophy in Alzheimer's disease or small vessel changes indicative of vascular dementia. Liver ultrasound can rule out complications such as hepatic or portal vein thrombosis and hepatocellular carcinoma. Additionally, vascular-phase abdominal CT scans are useful for identifying large spontaneous portosystemic shunts [4].

Neuropsychological Testing

Bedside neuropsychological tests, including the seven-pointed star test and the 'serial 7s' test, are effective in detecting neurocognitive dysfunction in cirrhotic patients suspected of having low-grade HE. The animal naming test, requiring patients to name 15 animals within one minute, is a quick and efficient method that discriminates between unimpaired and minimal or grade 1 HE patients. The European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) have issued guidelines detailing psychometric and neurophysiological tests for HE. These assessments should be conducted by trained professionals and are particularly valuable for patients whose quality of life, employment, or public safety may be affected.

Electroencephalography (EEG)

Electroencephalography can reveal triphasic waves in patients with advanced HE, although it lacks sensitivity in detecting minimal or low-grade HE. In select centers, advanced modalities such as visual, somatosensory, or auditory evoked potentials may offer greater diagnostic sensitivity; however, these techniques are not yet universally validated.

Management of Hepatic Encephalopathy (HE)

Addressing Precipitating Factors:

In patients with cirrhosis presenting with HE, identifying and managing precipitating factors is paramount. Common precipitating factors include infections, ammonia load (e.g., upper gastrointestinal bleeding or portocaval shunt), dehydration, hyponatremia, electrolyte imbalances, constipation, and the use of sedatives or opiate analgesics such as benzodiazepines. Each of these factors demands specific interventions to mitigate their impact on HE development or progression.

- **Infection**: A low threshold for initiating antibiotics is recommended, as approximately 40% of hospitalized cirrhotic patients experience sepsis or systemic inflammatory response syndrome, which can lead to organ failure and high mortality rates. Empirical administration of a broad-spectrum antibiotic for 3–5 days is advisable in the absence of positive microbial cultures, aligning with local microbiology guidelines when a septic focus is detected.

- **Gastrointestinal Bleeding**: An upper gastrointestinal bleed significantly increases the ammonia burden, often precipitating HE. Current evidence supports a 5-day course of empirical antibiotic therapy in cases of variceal bleeding to mitigate the risk of aspiration pneumonia and infection.

- **Constipation**: Enemas are effective in acute settings for improving consciousness levels. While lactulose is commonly used to manage HE by promoting two bowel movements per day, its use in acute HE is supported by limited evidence. Its side effects, including bloating and dehydration-induced diarrhea, may paradoxically heighten HE risk.

- **Electrolyte Disturbances**: Abnormalities, especially hyponatremia, should be promptly corrected. Hyponatremia often resolves with diuretic cessation and avoidance of intravenous glucose 5%. Intravenous normal saline (1 liter) facilitates renal ammonia excretion and is an effective yet underutilized treatment. In severe HE (grade 3/4), haemofiltration efficiently reduces blood ammonia concentrations, especially in cases of renal dysfunction.

Specific Interventions:

Targeted treatments for HE focus predominantly on the gut, given its role in ammonia production. Patients recovering from an HE episode must be counseled regarding driving risks and, in the UK, are required to notify the Driver and Vehicle Licensing Agency for a formal driving assessment.

- **Portosystemic Shunt Embolization**: Large portosystemic shunts (>8 mm) contribute to recurrent or persistent HE in cirrhotic patients. Clinical guidelines recommend shunt obliteration in patients whose HE persists despite standard therapy, provided their Model for End-stage Liver Disease (MELD) score is below 11, ensuring sufficient functional liver mass to accommodate redirected portal flow.

- **Non-absorbable Disaccharides**: Lactulose, a first-line therapy for HE for over four decades, has limited high-quality evidence supporting its acute HE use. While multicenter placebo-controlled trials are lacking, some studies suggest lactulose's efficacy in preventing overt HE recurrence over long durations.

- **Rifaximin**: This non-absorbable antibiotic is a robust adjunct to lactulose. A randomized controlled trial demonstrated that rifaximin effectively maintains remission and reduces HE-related hospitalizations. It is recommended as an add-on therapy by major guidelines for recurrent overt HE.

- **l-Ornithine l-Aspartate (LOLA)**: By enhancing the conversion of ammonia into urea and glutamine, LOLA serves as a potent ammonia-lowering agent in cirrhosis. Recent trials suggest that intravenous LOLA, in conjunction with lactulose and rifaximin, improves recovery and reduces mortality in severe HE.

- **Nutrition**: Malnutrition and sarcopenia exacerbate HE; thus, adequate protein and caloric intake must be maintained. Restrictive low-protein diets should be avoided [5].

Emerging Therapies:

Faecal microbiota transplantation (FMT), a novel intervention for gut dysbiosis, has shown promise in early-phase trials. Patients with cirrhosis and HE demonstrated enhanced gut microbiota diversity, improved mucosal biodiversity, and better cognitive outcomes post-FMT. However, further validation through randomized controlled trials is necessary before FMT can be integrated into routine HE management. This multifaceted approach, combining the management of precipitating factors, targeted treatments, and emerging therapies, provides a comprehensive framework for mitigating the burden of HE in cirrhotic patients.

Liver Transplantation and Related Considerations in Hepatic Encephalopathy (HE)

Liver Transplantation: The prognosis for patients with cirrhosis who experience their first episode of HE is poor, with transplant-free survival rates of only 42% at 1 year and 23% at 3 years. Early referral for liver transplantation evaluation is strongly recommended to improve outcomes. Timely intervention may provide these patients with a chance at prolonged survival and improved quality of life.

Prophylaxis of HE Before Transjugular Intrahepatic Portosystemic Shunt (TIPS) Placement: HE is a common complication after TIPS insertion, affecting 35–50% of patients, and is associated with a twofold increase in mortality for those experiencing early overt HE. Prophylactic measures can significantly reduce this risk. A large double-blind randomized controlled trial demonstrated that rifaximin, administered 14 days before TIPS placement, reduced the incidence of overt HE over the subsequent 168 days from 53% to 34%. These findings support the use of rifaximin as a preventive strategy in patients scheduled for TIPS.

Acute Liver Failure: Acute liver failure is a severe, life-threatening condition characterized by extensive liver injury and multisystem involvement. Early identification and referral to specialized centers with expertise in acute liver failure management are critical for patient survival. Key management strategies for patients with HE due to acute liver failure include:

- Preventing severe cerebral edema and intracranial hypertension.
- Maintaining sepsis-free conditions and ensuring adequate sedation.
- Reducing cerebral blood flow while avoiding hypo-osmolality.

Emergency liver transplantation has revolutionized the management of acute liver failure, becoming a standard of care for patients with a poor prognosis based on established criteria. This approach has significantly improved survival rates in this high-risk population. By integrating proactive transplantation referral, preventive strategies like rifaximin prophylaxis, and advanced interventions for acute liver failure, healthcare providers can better manage the complexities of HE and associated liver conditions.

Emergency Management of Hepatic Encephalopathy and Esophageal Varices

The emergency care of patients with hepatic encephalopathy (HE) and esophageal varices requires prompt, multidisciplinary intervention to stabilize the patient, address precipitating factors, and prevent life-threatening complications. In comatose patients with HE (grade 3/4), airway protection is paramount. Endotracheal intubation is often required to prevent aspiration and support ventilation. Simultaneously, precipitating factors such as infections, gastrointestinal bleeding, or electrolyte imbalances must be identified and managed. Broad-spectrum antibiotics are initiated to treat or prevent sepsis, especially in cases of spontaneous bacterial peritonitis (SBP). Correction of metabolic disturbances, including hyponatremia or hypokalemia, is critical for reducing HE severity. Measures to lower systemic ammonia levels include lactulose, administered orally, via nasogastric tube, or rectally, aiming to achieve 2–3 soft bowel movements daily. The addition of rifaximin, a non-absorbable antibiotic, complements lactulose by reducing ammonia-producing gut flora. Intravenous L-ornithine L-aspartate (LOLA) may also be administered to facilitate ammonia detoxification. Monitoring of vital signs, hemodynamic stability, and mental status is essential, with supportive care tailored to prevent further deterioration.

Esophageal variceal bleeding, a common precipitating factor for HE, demands urgent attention due to its high mortality risk. Initial management focuses on stabilizing the patient with fluid resuscitation using crystalloids or blood products, avoiding over-resuscitation to prevent worsening portal hypertension. Vasoactive agents such as terlipressin or octreotide are administered to reduce portal pressure and control bleeding. Emergency esophagogastroduodenoscopy (EGD), performed within 12 hours, is the cornerstone of intervention, with endoscopic band ligation being the preferred treatment for active bleeding. Sclerotherapy may be used if band ligation is unsuccessful or unavailable. In cases of massive or refractory bleeding, a temporary balloon tamponade using a Sengstaken-Blakemore tube may provide hemostasis until definitive therapy, such as a transjugular intrahepatic portosystemic shunt (TIPS), can be performed. Prophylactic antibiotic therapy, such as ceftriaxone, is standard to prevent SBP and systemic infections, which are frequent in these patients. Following stabilization, intensive care monitoring is crucial to address ongoing risks. Long-term management includes secondary prophylaxis with non-selective beta-blockers (e.g., propranolol) and periodic endoscopic surveillance to prevent rebleeding. Nutritional support must be optimized, as malnutrition and sarcopenia exacerbate HE and hinder recovery. For patients with recurrent HE or refractory variceal bleeding, liver transplantation should be considered as a definitive treatment. Early referral to a transplant center is essential, as survival after a first episode of HE is low, with transplant-free survival rates of only 42% at one year and 23% at three years. Comprehensive emergency management of HE and esophageal varices can significantly improve patient outcomes by addressing acute complications and facilitating long-term care planning [6].

Conclusion:

Hepatic encephalopathy (HE) remains a significant burden in patients with liver dysfunction, manifesting through a complex interplay of systemic and neurological factors. The multifaceted approach to managing HE emphasizes the importance of addressing precipitating factors, optimizing pharmacological interventions, and exploring innovative therapies. Established treatments, including lactulose and rifaximin, provide robust frameworks for maintaining remission and reducing hospitalizations. Emerging options such as l-ornithine l-aspartate and fecal microbiota transplantation (FMT) offer promising avenues to enhance therapeutic outcomes, particularly by targeting the gut-liver axis and restoring microbial diversity. The recognition and early treatment of precipitating factors, such as infections, gastrointestinal bleeding, and electrolyte imbalances, remain central to clinical management. A multidisciplinary approach that integrates neuropsychological assessments, imaging, and laboratory investigations ensures comprehensive evaluation and timely interventions. Furthermore, liver transplantation remains the definitive treatment for advanced HE, highlighting the need for early referral and evaluation in eligible patients. Research into novel interventions, particularly FMT and precision therapies targeting the gut microbiome, underscores the evolving landscape of HE management. These approaches have demonstrated potential in improving cognitive outcomes and quality of life, though further validation through randomized controlled trials is necessary. Preventive strategies, such as prophylactic use of rifaximin before transjugular intrahepatic portosystemic shunt (TIPS) placement, exemplify the importance of tailoring interventions to patient-specific risks. As HE research advances, integrating emerging therapies into clinical practice will be crucial for reducing its burden. Multidisciplinary care, patient education, and continuous research remain pivotal in improving prognosis and enhancing the quality of life for patients with HE. By bridging gaps in knowledge and adopting innovative strategies, healthcare professionals can mitigate HE's impact on this vulnerable population.

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الإدارة الطارئة للاعتلال الدماغي الكبدي: مراجعة محدثة

الملخص:

الخلفية :يُعتبر الاعتلال الدماغي الكبدي (HE) اضطرابًا عصبيًا نفسيًا يرتبط بخلل وظائف الكبد. يظهر في شكل اعتلال دماغي ظاهر أو طفيف، ويؤثر بشكل كبير على التنبؤ بمآل المرض، لا سيما في حالات تليف الكبد والفشل الكبدي الحاد. وعلى الرغم من التقدم الطبي، لا يزال الاعتلال الدماغي الكبدي يمثل تحديًا سريريًا نظرًا لتنوعه وتعقيداته في التشخيص والعلاج.

الهدف :استعراض وتلخيص الاستراتيجيات الطارئة لتشخيص وإدارة الاعتلال الدماغي الكبدي، بما في ذلك الأساليب السريرية والدوائية والعلاجات المبتكرة.

الطرق :تم إجراء تحليل شامل للأدبيات الحالية مع التركيز على أنظمة التصنيف الموحدة، وأساليب التشخيص، وبروتوكولات الإدارة. تشمل النقاط الرئيسية معالجة العوامل المسببة، واستخدام العلاجات الدوائية، واستكشاف العلاجات الناشئة مثل زراعة ميكروبيوتا الأمعاء.(FMT)

النتائج :تساعد المعايير الموحدة، مثل تصنيف "ويست هيفن"، في تقييم شدة الاعتلال الدماغي الكبدي. تظل التقييمات السريرية والنفسية العصبية أساسية، مدعومة بالتصوير الطبي والفحوصات المخبرية. تشمل الإدارة الفعالة علاج العوامل المسببة مثل العدوى، والنزيف المعوي، واختلال توازن الإلكتروليتات. تشمل الخيارات الدوائية اللاكتولوز، والريفاكسمين، والل-أورنيثين الل-أسبارتات التي تستهدف إزالة سمية الأمونيا. تُظهر العلاجات الناشئة مثل زراعة ميكروبيوتا الأمعاء إمكانيات واعدة لتحسين النتائج الإدراكية عبر استعادة تنوع ميكروبيوتا الأمعاء. ويظل زرع الكبد أمرًا حاسمًا للبقاء على قيد الحياة في الحالات المتقدمة.

الخاتمة :تتطلب إدارة الاعتلال الدماغي الكبدي نهجًا متعدد التخصصات يدمج التدخلات التقليدية والمبتكرة. يُعد علاج العوامل المسببة، وتحسين أنظمة العلاج الدوائية، واستكشاف العلاجات الجديدة أساسيًا لتحسين النتائج. ينبغي أن تركز الأبحاث المستقبلية على التحقق من فعالية العلاجات الناشئة ودمجها بشكل فعال في الممارسات السريرية.

الكلمات المفتاحية :الاعتلال الدماغي الكبدي، خلل وظائف الكبد، إزالة سمية الأمونيا، ميكروبيوتا الأمعاء، زراعة ميكروبيوتا الأمعاء، زرع الكبد.