MANAGEMENT OF PATIENTS WITH ACUTE HEPATIC ENCEPHALOPATHY

MODERN PRACTICE OF INTERNAL MEDICINE WITH EMERGENCY CONDITIONS

Guidelines for students and interns

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
Харківський національний медичний університет

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ВЕДЕННЯ ПАЦІЄНТІВ З ПЕЧІНКОВОЮ ЕНЦЕФАЛОПАТІЄЮ

СУЧАСНА ПРАКТИКА ВНУТРІШНЬОЇ МЕДИЦИНИ З НЕВІДКЛАДНИМИ СТАНАМИ

Методичні вказівки
для студентів та лікарів-інтернів

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Ведення пацієнтів з печінковою енцефалопатією. Сучасна практика внутрішньої медицини з невідкладними станами : метод. вказ. для студентів та лікарів-інтернів / упоряд. О. Я. Бабак, Н. М. Железнякова, А. С. Шалімова та ін. – Харків : ХНМУ, 2020. – 12 с.

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Management of patients with acute hepatic encephalopathy

Number of hours: Classroom work – 6:00, independent work – 3:00

Material and methodological support of the theme: table, multimedia presentation, laboratory data and instrumental methods of investigation.

Justification threads. Hepatic encephalopathy is a syndrome observed in patients with cirrhosis. Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction, after exclusion of other known brain disease. Hepatic encephalopathy is characterized by personality changes intellectual impairment, and a depressed level of consciousness. An important prerequisite for the syndrome is diversion of portal blood into the systemic circulation through portosystemic collateral vessels. Hepatic encephalopathy is also described in patients without cirrhosis with either spontaneous or surgically created portosystemic shunts. The development of hepatic encephalopathy is explained, to some extent, by the effect of neurotoxic substances, which occurs in the setting of cirrhosis and portal hypertension.

The purpose of the activity:

- General: The students should be able to describe main links of pathogenesis, clinical features, diagnostic and treatment of hepatic encephalopathy.
- Specific: Provide a basic overview of the pathophysiology, diagnosis, and classification of hepatic encephalopathy; evaluate guideline-based management strategies for the treatment of hepatic encephalopathy; develop an individualized pharmacotherapy and monitoring plan for the management of hepatic encephalopathy, when given specific patient information.

Specific objectives: The student should know:	**Initial level of knowledge – abilities: The student should be able to:**
• Describe the hepatic encephalopathy. • Describe the main mechanism of ethiopathogenesis. • Describe the main clinical features of hepatic encephalopathy. • List and describe the group of drugs that are used in the treatment of hepatic encephalopathy and give specific examples of each. • Make a treatment plan of patient with hepatic encephalopathy	• analyze the complaints and anamnesis of patients. • recognize the clinical signs. • make a plan of examination of patients. • diagnose the main causative diseases and conditions. • interpret the data of instrumental and laboratory research techniques; • differential diagnosis of condition. • assess the possible complications as well as to evaluate the prognosis of these patients. • provide medical aid to the patient. • prescribe drugs, which are used in such patients • assess the patient's prognosis

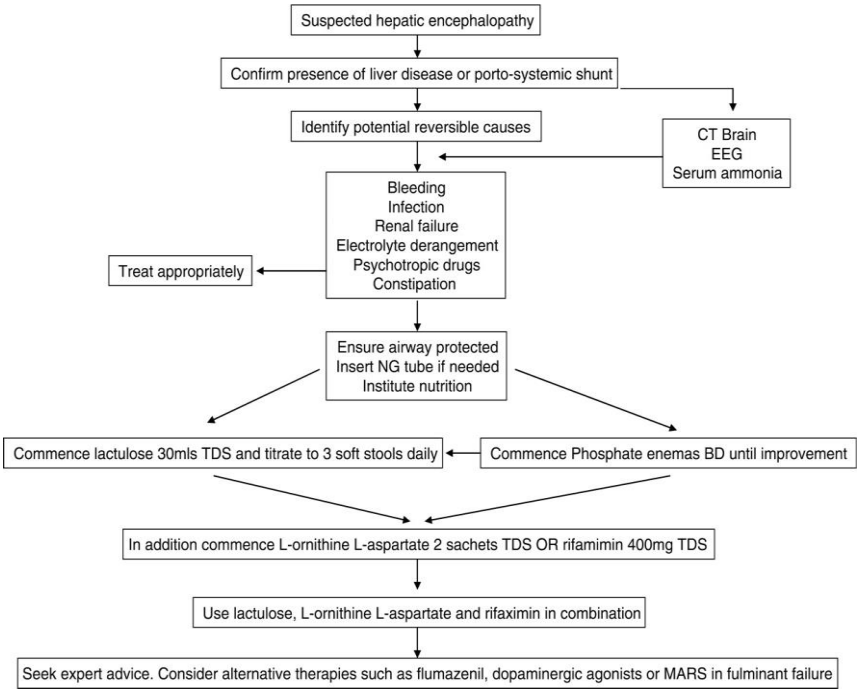
List of practical skills that students must master:

1. Evaluation of patients with hepatic encephalopathy.
2. Interpretation of laboratory data that reflect pathology causing hepatic encephalopathy.
3. Interpretation of tool data that reflect pathology leads to hepatic encephalopathy.
4. Working out the scheme of diagnostic plan.
5. Prescribing basic treatment.

Materials for the self-study:

- Improving the interpretation of ultrasound examination data.
- Improving the interpretation of the results of laboratory methods (ALT, AST, creatinine, bilirubin with fractions, coagulation).

Graphological structure of the topic



Indicative map of the work of students:

a) diagnosis criteria for checking them at the bedside;

b) choice of the most knowledgeable tests, laboratory and instrumental studies (possibly performed by students), confirming the diagnosis;

c) the appointment of treatment; prescribing (knowledge of the mechanism of action of drugs)

d) the choice of method of physical therapy treatment;
d) determining the prognosis and the patient's ability to work;
g) definition of disability;
c) disease prevention.

Hepatic encephalopathy (HE), or portosystemic encephalopathy, is a potentially reversible syndrome of impaired brain function in patients with progressive liver failure. However, HE is not a single category and may reflect the clinical manifestations of reversible metabolic encephalopathy, cerebral atrophy as a result of hepatocerebral dystrophy, cerebral edema, or any combination of these conditions. The mechanisms that impair the function of the brain in liver failure are still not fully understood, but it is clear that they are directly related to liver failure and impaired ammonia metabolism. If the underlying liver disease does not respond to treatment, HE is associated with poor survival and a high risk of recurrence. Even in the mildest form of HE, it reduces health-related quality of life and is a risk factor for episodes of severe HE.

Pathogenesis

Despite more than 100 years of research history, the pathogenesis of HE is still not entirely clear. This is mainly due to the difficulties in studying the brains of patients with HE in vivo. Most of the published data are derived from experimental HE models, which are far from perfect. The most common hypotheses of pathogenesis reflect the role of neurotoxins, impaired neurotransmission due to metabolic disorders in liver failure, changes in energy metabolism of the brain, amino acid imbalance, systemic inflammatory response, and impaired blood-brain barrier permeability. The various hypotheses for the pathogenesis of HE are not mutually exclusive. It is likely that many of the described disorders can act simultaneously and ultimately lead to the development of HE.

Neurotoxins. The most studied neurotoxin associated with HE is ammonia, which is produced primarily in the gastrointestinal tract and enters the liver via the portal vein. A healthy liver detoxifies the ammonia entering it by converting it to glutamine, thereby preventing its penetration into the systemic circulation. In progressive liver diseases, an increase in the concentration of ammonia in the blood occurs both as a result of a violation of its conversion by the liver to glutamine, and as a result of port-system shunting, in which blood, bypassing the liver, enters the systemic circulation.

With an increase in the concentration of ammonia in the blood, it penetrates the blood-brain barrier and has a neurotoxic effect primarily on astrocytes, the most numerous brain cells closely associated with the functioning of neurons. The key mechanism for the development of HE is astrocyte edema due to hyperammonemia.

Excess ammonia leads to the accumulation of glutamine formed in astrocytes, which is accompanied by an increase in intracellular osmolarity and, in high concentrations, causes cerebral edema.

Impaired neurotransmission. An important role in the pathogenesis of HE is played by impaired functioning of neurotransmitters of the cerebral cortex

and their receptors. In experimental models of liver failure, disorders of several neurotransmitter systems have been studied. Most of these works describe changes in the GABAergic neurotransmitter system, dopaminergic, serotonergic, and glutamatergic neurotransmitter systems. In particular, the role of GABAergic influences in the development of HE may be associated with the activation of benzodiazepine receptors in the brain and the associated increase in the synthesis of neurosteroids.

Amino acid imbalance. An important role in the pathogenesis of HE is played by amino acid imbalance in the form of an increase in the level of aromatic amino acids (tyrosine, phenylalanine, tryptophan), which are precursors of false neurotransmitters, and a decrease in the content of branched-chain amino acids (valine, leucine, isoleucine). Under these conditions, there is an excessive supply of aromatic amino acids to the brain, which serve as the initial product for the synthesis of false neurotransmitters. These shifts in amino acid composition are also accompanied by a decrease in dopamine synthesis, which also promotes the formation of false neurotransmitters.

Clinic

The clinical picture in HE is a wide range of non-specific neurological and mental disorders. Signs of encephalopathy in patients with chronic liver diseases depend on the etiology of the underlying disease, the nature and severity of pathogenic factors.

The severity of HE varies from latent (stage 0) and mild (stage I) to coma (stage IV). With minimal HE, it is manifested mainly by violations of abstract thinking and a general mild decrease in cognitive functions without impairment of memory, intelligence, speech, learning ability, which remain intact for a long time. In some patients with hepatic insufficiency, for a number of years, only violations of the higher brain functions have been detected without any other neurological symptoms.

As HE progresses, personality changes such as apathy, irritability, and decreased control over behavior increase, and clear changes in consciousness and motor function appear. Disturbances in the sleep-wake cycle with excessive daytime sleepiness are common, although complete disturbances in the sleep-wake cycle are usually absent. With an increase in liver failure, progressive disorientation in time and space develops, behavior disorder, episodes of confusion with agitation or drowsiness, stupor and, finally, coma occur. In the consensus of the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN), the appearance of disorientation or asterixis ("flapping" tremor) is considered as the initial signs of overt HE.

In non-comatose HE patients, motor dysfunctions such as muscle hypertension, hyperreflexia, and positive Babinsky reflex are observed. With the development of coma, deep tendon reflexes usually diminish and even disappear, although pyramidal signs may persist. Focal neurological deficits can sometimes occur. Seizures in HE are very rare.

Frequent manifestations of the disease are extrapyramidal disorders in the form of facial hypomimia, muscle rigidity, bradykinesia, hypokinesia, monotony

and slowing down of speech, parkinson-like tremor and dyskinesia with limited voluntary movement.

Asterixis ("flapping tremor") is often noted in the early and middle stages of HE, which precede stupor or coma. In reality, it is not a tremor, but a negative myoclonus and is caused by hyperextension of the patient's wrist with the fingers apart. It is noteworthy that mental and motor disorders in HE may be insignificant or do not progress in the same way in different patients, which leads to difficulties in determining the stage of HE.

Classification

According to the practical recommendations of the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver HE is classified according to four criteria: depending on the reasons that led to its development; by the duration and nature of the flow; by the severity of the course (stages) and depending on the presence of provoking (trigger) factors.

A – hepatic encephalopathy as a result of acute hepatic failure;

B – portosystemic shunting in the absence of liver cirrhosis (LC);

C – hepatic encephalopathy in patients with cirrhosis.

Classification of HE by the duration and nature of the flow:

1) episodic HE;

2) recurrent HE - these are attacks of HE that occur at intervals of 6 months or less;

3) persistent HE represents behavioral disturbances that are constantly present and interspersed with relapses of overt HE.

Classification of the severity of the course of HE by stages (West Haven scale)

I. Minimum (latent) stage: there is no clear clinical symptomatology, but there is a violation of standardized psychomotor tests (number link test, line test).

II. The first (mild) stage: apathy, agitation, irritability, anxiety, euphoria, fatigue, disturbances in the rhythm of sleep and wakefulness, slight tremor, impaired coordination of movements, asterixis.

III. Second (middle) stage: drowsiness, lethargy, disorientation in time and space, inadequate behavior, asterixis, dysarthria, ataxia.

IV. The third (severe) stage: stupor, pronounced disorientation, fuzzy speech, hyperreflexia, the presence of pathological reflexes (Gordon, Zhukovsky), myoclonus, hyperventilation.

V. Fourth stage: hepatic coma, decerebral rigidity, oculocephalic phenomenon, lack of response to any stimuli.

Depending on the presence of provoking (trigger) factors, HE is subdivided into unprovoked and provoked (in this case, the provoking factor must be indicated). It is advisable to identify provoking factors (infections, gastrointestinal bleeding, diuretic overdose, electrolyte disturbances, constipation) for all episodes of type C HE and to eliminate them if present.

Diagnostics

Diagnosis of overt HE. The diagnosis of overt HE is based on physical examination. It includes assessing the symptoms of HE as well as excluding other causes of impaired brain function. In the clinical picture, patients with overt HE have symptoms of diseases of the hepatobiliary system, for example, in most patients, the development of HE is preceded by jaundice. Liver odor and hyperventilation can often be detected in patients with encephalopathy. Also, the diagnosis of HE is confirmed by the identification of provoking factors (infection, bleeding and constipation, etc.).

The West-Haven criteria are the gold standard for diagnosing overt HE, but they have limited diagnostic value due to subjective assessments, especially in stage I HE, since mild hypokinesia, psychomotor retardation and absent-mindedness can be missed on clinical examination. The leading diagnostic symptoms of overt HE are disorientation and asterixis in the patient.

It is recommended to use the Glasgow Coma Scale (GCS) to describe the condition of patients with significantly altered consciousness. The Glasgow scale provides for the calculation of points reflecting the severity of the patient's reaction to stimuli. Determine the ability to open the eyes, the nature of motor and verbal reactions to simple stimuli (voice circulation and pain). Coma is preceded by less deep forms of oppression of consciousness: confusion, stupor and stupor.

Diagnosis of minimal HE. Minimal HE is defined as abnormalities in brain function on tests in patients with chronic liver disease who are not disorientated or have developed asterixis. The examination of such patients can include two main types of tests: psychometric and neurophysiological. ISHEN recommends using at least two tests, depending on availability and local conditions. The importance of testing for minimal HE is that it predicts the development of overt HE.

For the diagnosis of minimal HE, it is recommended to conduct neurophysiological and psychometric tests, among which the most important are both simple ones performed on paper with a pen (psychometric HE scale) and computerized (reaction time delay test, Stroop test, inhibitory control test and SCAN test) and neurophysiological (test of the critical flicker fusion frequency) tests. Electroencephalography can detect changes in the cortical activity of the brain in PE, but this method is not specific enough, since it can be influenced by concomitant metabolic disorders and drug intake.

Laboratory tests. In patients with HE, serum-biochemical hepatic syndromes of varying severity are revealed, depending on the predominant direction of pathological processes in the liver.

Syndrome of cytolysis, or syndrome of damage to hepatocytes (violation of integrity, necrosis of hepatocytes), is characterized primarily by an increase in aminotransferases (aspartate and alanine aminotransferase), as well as other enzymes – lactate dehydrogenase-5, aldolase, ornithinecarbamyltransferase, sorbitan dehydrogenase, gidrogeneta.

Cholestasis syndrome is characterized by an increase in bilirubin, mainly conjugated (direct), alkaline phosphatase, gamma-glutamyl transpeptidase, 5-nucleotidase, cholesterol and bile acids.

The syndrome of inflammation is characterized by an increased content of various fractions of globulins, dysproteinemia, and an increase in the content of serum immunoglobulins.

The AASLD/EASL guidelines note that in patients with chronic liver disease, only high blood ammonia levels are of diagnostic or prognostic value. However, if the ammonia content is within the normal range, the diagnosis of HE is questionable. Repeated ammonia measurements can be used to evaluate the effectiveness of treatment when patients are taking medications that lower their ammonia levels.

Computed tomography or magnetic resonance imaging and other imaging techniques do not provide complete diagnostic information and are of limited value. They are mainly used to exclude structural damage to the brain in patients with LC.

Differential diagnosis

The AASLD/EASL guidelines point to the need to exclude other diseases that may resemble HE:

1) diabetes mellitus (hypoglycemic, hyperglycemic and hyperosmolar coma, lactic acidosis);

2) alcohol abuse (intoxication, withdrawal syndrome, Wernicke's syndrome);

3) overdose of drugs (benzo-diazepines, neuroleptics, opioids);

4) neuroinfections and electrolyte disturbances (hyponatremia, hypercalcemia);

5) non-convulsive epilepsy, mental illness;

6) intracerebral hemorrhage and ischemic stroke;

7) dementia (primary and secondary);

8) brain damage (traumatic, neoplastic, normotensive hydrocephalus, obstructive sleep apnea syndrome).

Treatment

Treatment for HE includes elimination of provoking factors, dietary interventions, and drug therapy. Elimination of provoking factors is a priority in the treatment of overt HE, since in 90% of patients this is sufficient to improve the condition.

Diet

Correction of impaired protein-nitrogen metabolism is critical in the treatment of all stages of HE, since 75 % of patients with HE have moderate or severe protein-energy deficiency, accompanied by loss of muscle mass. Prolonged restriction of protein intake is harmful for patients with HE, since the need for protein in these patients is relatively higher than in healthy individuals.

Therefore, according to the AASLD / EASL recommendations, daily energy intake should be maintained at 35–40 kcal per kg of body weight, and daily protein intake should be in the range of 1.2–1.5 g/kg. Restricting protein intake is recommended only for the first few days after the onset of HE, but then this

measure should be abandoned. Animal proteins should be substituted for dairy and vegetable proteins, and foods enriched with branched chain amino acids should be consumed.

Drug therapy

Drug therapy is an important part of the management of overt HE. With minimal HE in the absence of its clinical manifestations, pharmacotherapy is usually not used. At the same time, it can be assigned to this category of patients in cases of a noticeable effect of minimal HE on the quality of life. Various drugs (nonabsorbable disaccharides, antibiotics, branched-chain amino acids, L-ornithine-L-aspartate) can be used to correct HE, with varying levels of evidence of efficacy.

Non-absorbable disaccharides. Lactulose is a synthetic disaccharide that inhibits the formation of ammonia. Lactulose is the first choice in the treatment of overt HE. Lactulose syrup is prescribed 25 ml every 1–2 hours until at least 2 bowel movements appear with soft or loose stools throughout the day. In the future, the dose of the drug is titrated individually to maintain 2- or 3-fold bowel emptying during the day. Reception of excessively high doses of lactulose can lead to complications such as aspiration, dehydration, hypernatremia, irritation of the perianal skin, and in some cases even exacerbate the course of HE.

Antibiotics. Rifaximin is a non-absorbable antibiotic that inhibits the ammoniogenic proteolytic bacterial intestinal microflora. A number of studies have shown the effectiveness of rifaximin in the treatment of HE. According to the AASLD/EASL recommendations, rifaximin is an effective adjunct to lactulose for the prevention of recurrence of overt HE. In comparative studies, 3–6 months of rifaximin therapy improved cognitive function and decreased the level of ammonia in patients with HE. Rifaximin is prescribed at a dose of 200-400 mg 2–3 times/day (1 200 mg/day) for 5–7 (up to 14) days.

Of the other antibiotics, neomycin is still used to treat HE, metronidazole can be used for short-term therapy, but long-term use of these drugs is limited due to side effects

Branched-chain amino acids. A number of studies have shown the effectiveness of nutritional therapy with the consumption of food enriched with branched-chain amino acids. Due to the predominant assimilation of these amino acids, the relative content of aromatic amino acids, which serve as precursors of false neurotransmitters, decreases. In addition, branched-chain amino acids contribute to an increase in muscle mass, as a result of which the detoxification of ammonia, which partly occurs in skeletal muscle, is enhanced. The AASLD/EASL guidelines only provide for oral administration of branched-chain amino acids as an alternative or adjunctive treatment for patients who do not respond to conventional therapy.

L-Ornithine-L-Aspartate (LOLA). Since ornithine and aspartate play a major role in the conversion of ammonia to urea, LOLA supplementation can help reduce the clinical manifestations of HE. Over the past 10 years, several randomized

studies have been carried out, the results of which have shown the high efficacy and safety of this drug in the treatment of HE. LOLA is available as a solution for intravenous infusion and as a granulate for oral administration. The standard regimen provides for intravenous drip of 20–30 g of the drug for 7–14 days, followed by a switch to oral administration of 9–18 g/day. To achieve a faster and more lasting result, a combination of intravenous and oral administration is possible.

Flumazenil is a benzodiazepine receptor antagonist that directly affects the functions of the central nervous system. Flumazenil is used quite rarely, since by giving a short-term effect of restoring consciousness, it only contributes to a transient improvement in the mental state, but does not affect recovery and survival rates

The effectiveness of the therapy is determined by the reverse development of clinical symptoms. In acute liver failure with the development of hepatic coma and cerebral edema, treatment is carried out in the intensive care unit using the same pharmaceuticals as in chronic liver failure, but in higher doses.

Liver transplantation for cirrhosis with recurrent, poorly amenable to conservative therapy of HE can increase the life expectancy of patients. The average 5-year survival rate of patients after transplantation exceeds 72 %

Tasks for independent work:

1. What is the definition of hepatic encephalopathy?
2. What are the main causes of hepatic encephalopathy?
3. What are the main pathogenetic links of hepatic encephalopathy?
4. What are the main types of hepatic encephalopathy?
5. What are the clinical features of different hepatic encephalopathy grade?
6. What laboratory tests are used in patients with hepatic encephalopathy?
7. What imaging studies are used in patients with hepatic encephalopathy?
8. What treatment methods are used to decrease intestinal ammonia production in patients with hepatic encephalopathy?
9. What treatment methods are used to increase ammonia clearance in patients with hepatic encephalopathy?
10. What treatment methods are used to improve sleep disturbances in patients with hepatic encephalopathy?

Tests

1. Patient K., 34, suffers from liver cirrhosis; recent relatives were seen in patient apathy, agitation, anxiety, euphoria, fatigue, disorders of sleep rhythm. On examination determined: light tremor, impaired coordination. What is the complication that appears to have the patient?

a. Portal hypertension
b. Hepatic encephalopathy
c. Ascites-peritonitis
d. Bleeding from the esophagus veins
e. Hepatorenal syndrome

2. Patient S., aged 52, was admitted to hospital with complaints on general weakness, weight loss, weight in the right upper quadrant, jaundice. Abuse alcohol. On examination the doctor was suspected latent hepatic encephalopathy. What research should be carried out to confirm the diagnosis?

a. Ultrasonography of the abdomen *d. CT of the abdomen*
b. Standardized psychometric tests *e. Liver biopsy*
c. Electroencephalography

3. Patient S., 31-year stays in the hospital with a diagnosis of liver cirrhosis of viral etiology. At the 7 th day appeared inadequate behavior, euphoria, changes in sleep rhythm, liver breath, tremor of the limbs. Liver on the costal arch edge. What you want to assign the patient to relieve symptoms of complications?

a. Antiviral drugs + deintoxication therapy
b. Blood transfusion + antiviral drugs
c. Lactulose + antibiotic + deintoxication therapy
d. Hepatoprotectors + deintoxication therapy
e. Glucocorticoids + lactulose

4. Patient R., 50, a long-time suffering from liver cirrhosis was admitted to hospital due to acute developed symptoms of hepatic encephalopathy. On examination determined spoor, expressed disorientation, unclear speech, hyperreflexia, pathologic reflexes (Gordon, Babinsky, Zhukovsky), myoclonus, hyperventilation. What stage of hepatic encephalopathy occurs?

a. Subclinical *b. Stage 1* *c. Stage 2* *d. Stage 3* *e. Stage 4*

5. Patient K., 44, suffers from liver cirrhosis, in recent days the apathy, agitation, anxiety, euphoria, fatigue, disorders of sleep rhythm. On examination determined: light tremor, impaired coordination. Doctors suspected hepatic encephalopathy. Differential diagnosis of this condition should be conducted with all the listed pathologies, EXCEPT for:

a. Delirium tremens *c. Subdural hematoma* *e. Portal hypertension*
b. Wernicke syndrome *d. Intracranial abscess*

RECOMMENDED LITERATURE

Main references

1. Current Medical Diagnosis and Treatment 2016 /Michael W. Rabow, M. Papadakis, Stephen J. McPhee. – 2015. – 1920 p.
2. Harrisons Manual of Medicine, 20th Edition / Dennis L. Kasper, Anthony S. Fauci, Stephen L. Hauser, Dan L. Longo, J. Larry Jameson, Joseph Loscalzo. – 2020. – 1351 p.
3. Harrisons Principles of Internal Medicine Self-Assessment and Board Review 19th Edition / Dennis Kasper, Joseph Loscalzo, J. Jameson, Anthony Fauci, Stephen Hauser, Dan Longo. – 2015. – 3000 p.

Additional references

1. Mayo Clinic Internal Medicine Board Review. 12th. / Edited by Christopher M. Wittich. – 2020. – 936 p.
2. The Washington manual gastroenterology subspecialty consult. Fourth Edition. / Edited by C. Prakash Gyawali. – 2020. – 366 p.

Навчальне видання

ВЕДЕННЯ ПАЦІЄНТІВ З ПЕЧІНКОВОЮ ЕНЦЕФАЛОПАТІЄЮ

СУЧАСНА ПРАКТИКА ВНУТРІШНЬОЇ МЕДИЦИНИ З НЕВІДКЛАДНИМИ СТАНАМИ

Методичні вказівки для студентів та лікарів-інтернів

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