Ped. Acute Liver Failure

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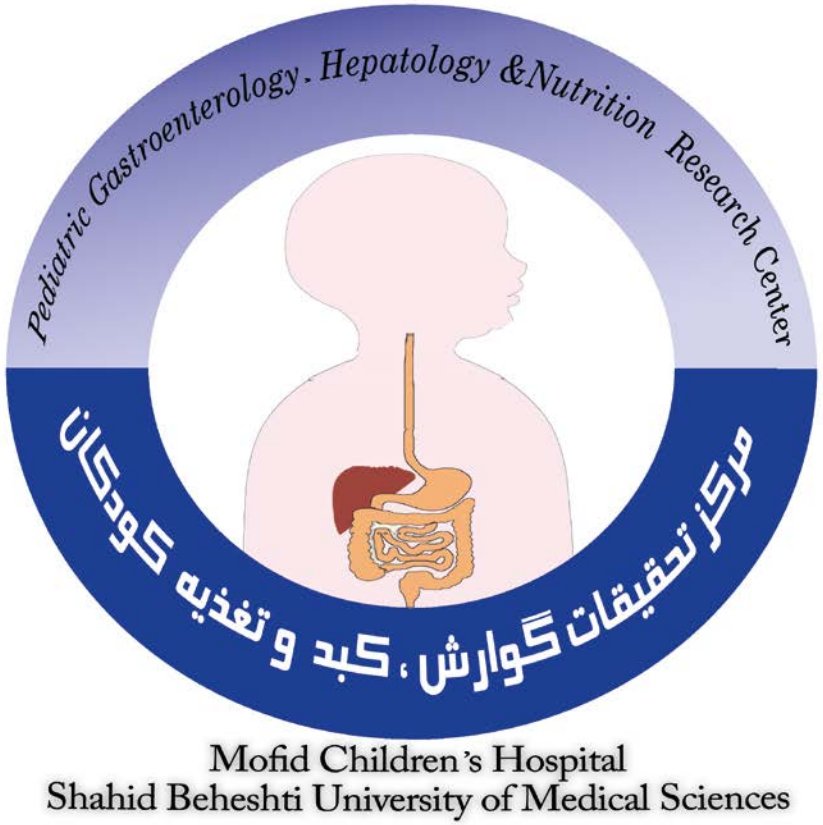
Fellowship of Pediatric Gastroenterology



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Introduction

Pediatric ALF is not a single diagnosis.

Pediatric ALF is a complex, rapidly progressive clinical syndrome.

Is the final common pathway for many disparate conditions.

<u>Frequency</u> in all age groups in the USA 17/ 100 000/ yr.

Frequency <u>in children is *unknown*</u>.

ALF accounts for 10 - 15% of ped. Liver transplants performed annually.

Management requires a *multidisciplinary team*.

Pressing clinical questions:

Is the condition treatable?

Risk of deterioration or improvement on each day the child is alive with his/her *native* liver?

Possibility of the full recovery without a liver transplantation.

Are associated morbidities recoverable or irreversible?

Definition of ped. ALF

In adults

First signs of hepatic dysfunction ----------HE

↑

Less than 8 weeks

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In children

1. HE is difficult to assess in children and may not be clinically apparent until the terminal stages of the disease process.
2. In setting of ALF mental status changes caused by infection, metabolic derangements, anxiety associated with acute illness is not descernable from liver – based encephalopathy.
3. The onset of jaundice is a time point that is difficult to define as it is dependent on clinical observation by individuals with disparate expertise in assessing jaundice. And jaundice may go undetected for a period of time.

Entry criteria

1. Children with no known evidence of chronic liver disease
2. Biochemical evidence of acute liver injury
3. Coagulopathy not corrected by vitamin K

- PT: 15 (20 without HE)
- INR : 1.5 (2.0 without HE)

Clinical Characterization

A previously healthy patient typically experiences a non-specific prodrome include :

x. Abdominal discomfort

ц. Malaise

ц. Fever +/-

Symptomes :

- **Persist**
- **Wax and wane**

<u>Precise onset</u> of disease is rarely identified (unless acute ingestion of e.g mushrooms, acetaminophen…)

Etiology

- Acetaminophen
- Medication (non-acetaminophen) or toxin
- Immune dysregulation

1. Autoimmune marker positive
2. Hemophagocytic lymphohistiocytosis
3. Neonatal hemochromatosis

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- **Inheridate metabolic disease**
- **Infectious diseases**

1. Hepatitis viruses

2. Infection with viruses other than hepatitis viruses

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3. Non-viral infectious hepatitis :

a) Nisseria meningitides
b) Septic shock
c) Intra-abdominal abscesses
d) Portal sepsis with enteric organisms
e) Spirochetal infection
f) Congenital syphilis
g) Leptospirosis
h) Brucella spp
i) Coxiella burnetii (Q fever)
j) Plasmodium falciparum
k) EH (Entamoeba Histolytica)

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- **Indeterminate failure (50%)**

نکته های استامینوفن

از هر بیمار مبتلا به نارسایی حاد کبد باید تاریخچه مصرف استامینوفن سوال شود :

۱- یا به تنهایی دریافت شده یا در همراهی با دکونژستان ها / نارکوتیک ها.

۲- گاه حتی در دوزهای درمانی می تواند هپاتوتوکسیک باشد.

۳- ممکن است با مصرف تعمدی تک دوز هپاتوتوکسیک (< ۱۰۰ میلیگرم / کیلوگرم) مواجه باشیم یا مصرف غیر عمدی.

۴- گاهی مصرف مزمن استامینوفن مطرح است در دوزهای ۱۰۰ میلیگرم / کیلوگرم / روزانه.

۵- از مصرف همزمان سایر هپاتوتوکسیک ها هم باید پرسید.

☼ دو کلید هپاتوتوکسیسیتی استامینوفن :

آنزیم ها در حد ۱۰۰۰۰ بالا می روند اما افزایش بیلیروبین نهایت تا ۱۰ است.

در بیوپسی کبد ، نکروز سنتری لوبولر داریم.

کلیدهای بیوپسی داروهای غیر استامینوفن

1. Drug inducsed hepatitis: INH , PTU , Halothane
2. Cholestasis : Oxacillin
3. Steatosis : Sodium valproate , Amiodarone
4. Mixed hepatitis + cholestasis : Sulfa drugs

HLH Criteria (5 of 8)

Clinical Criteria :

- ❑Fever (> 7 ds)
- ❑Splenomegaly

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Laboratory Criteria:

- Bicytopenia without marrow hypoplagia , including:
  - HGB< 9
  - Plt< 100 000
  - PMN< 1000
- TG>/= 265 and/or Fibrinogen</= 150
- Hemophagocytosis in the BM, spleen or LN without evidence of malignancy
- Low or absent NKC cytotoxicity
- Ferritin>/= 500 ng/Ml
- Elevated soluble CD25 (IL-2R□chain; >/= 2400U/Ml)

Ethiology of ALF In < 3mo

1. HSV blood PCR (or HSV IgM, viral culture of blood or CSF, CSF PCR)
2. Enterovirus PCR
3. Lactate, Pyruvate (mitochondrial dis.)
4. Plasma Acylcarnithin Profile (FAOD)
5. Ferritin(Neonatal ISD Screen)
6. Serum AA profile (UCD/Metabolic)
7. Confirm newborn screen results (Galactosemia)
8. Confirm maternal HBV serology
9. Echocardiography and Abdominal US & Doppler (Vascular/Anatomic)

Ethiology of ALF In 3mo-4yr

1. HBS Ag, HAV IgM, EBV (VCA IgM or EBV PCR)
2. Lactate, Pyruvate (Mitochondrial dis.)
3. ANA, ASMA, ALKM, IgG (AutoImmune Hepatitis)
4. Drug Hx and Acetaminophen level
5. Plasma Acylcarnithine Profile (FAOD)
6. Serum AA Profile
7. Abdominal US & Doppler

Ethiology of ALF In 5yr-18yr

1. HBSAg, HAV IgM, EBV (VCA IgM or PCR)
2. ANA, ASMA, ALKM, IgG (AIH)
3. Ceruloplasmin (WD)
4. Drug Hx, Acetaminophen level
5. Lactate, Pyruvate (Mitochondrial)
6. Plasma Acylcarnithine Profile (FAOD)
7. Serum AA Profile
8. Abdominal US & Doppler

Metabolic Dis. Presenting as ALF <6mo

1. Galactosemia ---------- Urine RS
2. Neimann-Pick Type C ---------- Filter paper

در گیلان، مازندران، ایلام و لرستان دیده می شود/آتوزومال مغلوب است و در ازدواجهای فامیلی اتفاق می افتد.

1. Tyrosinemia ---------- HPLC/USA
2. Glycosilation Defect ----------
3. Mitochondrial Dis. ---------- Lactate, Pyruvate

در ماه های نخستین عمر موارد متابولیک که منجر به نارسایی حاد کبد می شوند شامل *گالاکتوزمی* ، *تیروزینمی* ، *میتوکندریال* و *نیمن پیک* هستند.

☼ کلید *گالاکتوزمی* = تاریخچه مصرف شیر واجد لاکتوز + سپسیس گرم منفی + مواد احیاکننده در ادرار + نارسایی حاد کبدی.

☼ کلید *تیروزینمی* = کو آگولوپاتی + سپسیس گرم منفی + آمینوترنسفراز نرمال یا نزدیک به نرمال

☼ کلید هپاتوپاتی *میتوکندریال* = نقایص نرولوژیک پیشرونده + کاردیومیوپاتی + میوپاتی + لاکتیک اسیدوزیس + نسبت لاکتات به پیرووات > ۲۵ مول/ مول

☼ کلید *نیمن پیک* = اسپلنومگالی

Metabolic Dis. Presenting as ALF In 7mo-4yr

1. Mitochondrial ---------- Lactate, Pyruvate
2. Tyrosinemia ---------- HPLC/USA
3. Alpha-1 AT Defficiency ---------- Alpha-1AT (Genotype/Phenotype)
4. Hereditary Fructose Intolerance ---- Urine RS
5. Urea Cycle Defect ---------- BUN/HPLC

در بچه های شیرخوار بزرگتر و کودکان تا ۵ سالگی بیشتر *اختلالا ت سیکل اوره* ، *تیروزینمی* ، *میتوکندریال و عدم تحمل ارثی فروکتوز* مطرح اند.

☼ کلید *اختلالا ت سیکل اوره* = هایپرآمونمی + تغییرات وضعیت منتال + تشنج + اما میبینید که تست های فانکشن کبد خوبند (یعنی ظن هپاتیک انسفالوپاتی نمی رود.)

☼ کلید *عدم تحمل ارثی فروکتوز* = زمان شروع علایم است که بعد از شروع فروکتوز و سوکروز است و نه زودتر.

Metabolic Dis. Presenting as ALF In 5-18yr

1. **Wilson Disease** ---------- Ceruloplasmin
2. Mitochondrial ---------- Lactate, Pyruvate
3. Fatty Liver of Pregnancy ---------- LFT

در سنین بالای ۵ سال شایعترین بیماری متابولیک همراه با نارسایی حاد کبد ، *ویلسون* است. اما اختلال *اکسیداسیون اسیدهای چرب* هم ذکر شده.

☼ کلید های *ویلسون* : آنمی همولیتیک کومبس منفی + هایپربیلیروبینمی + آلکالین فسفاتاز کاهش یافته + سرولوپلاسمین کاهش یافته سرم

In adults :

Alp : Bil < 4 and AST : ALT > 2.2

Diagnostic approach

Hx

- Onset of symptoms such as jaundice
- Change in mental status
- Easy bruising
- Vomiting
- Fever

- **Exposure to contact with infectious hepatitis**
- **Hx of blood transfusions**
- **Prescription and over – the – counter medications in the home**

- **F/H of:**

1. **Wilson disease**
2. **α-1 AT deficiency**
3. **infectious hepatitis**
4. **infant deaths**
5. **or autoimmune conditions**

- **Evidence of NDD/seizures**

- **Evidence of a chronic liver condition with an acute presentation:**

1. **Pruritus**
2. **Ascites**
3. **Growth failure**

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Ph/Ex

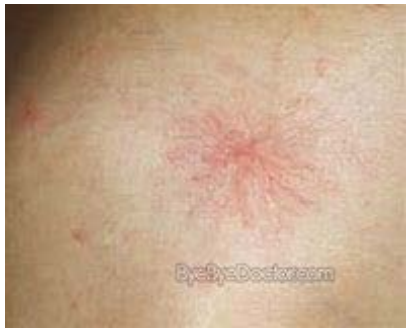
- Evaluation of growth/ development/ nutrition status
- Evidence of jaundice/ bruises/ bleeding following venipuncture/ petechiae
- Hepatomegaly +/- splenomegaly/ ascites/ peripheral edema
- Kayser-Fleischer rings are present in only 50% of patients with Wilson disease who present with ALF
- Fetor hepaticus associated HE is rarely present

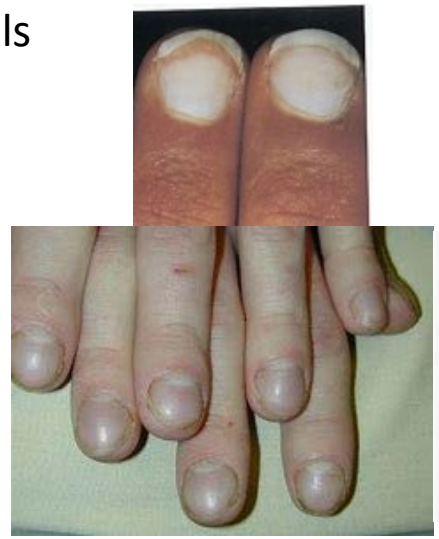
- Stigmata of chronic liver disease = Long-standing portal HTN = Include:

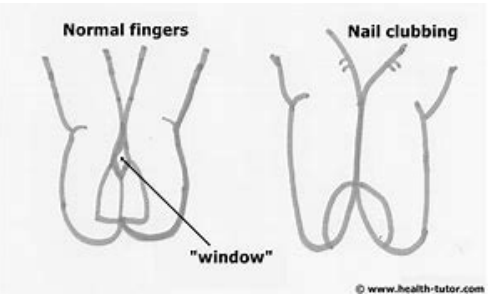
1. Digital clubbing
2. Palmar erythema
3. Cutaneous xanthoma
4. Prominent abdominal vessels

- Altered mental status should be assessed but may be difficult to assess in infants and young children.

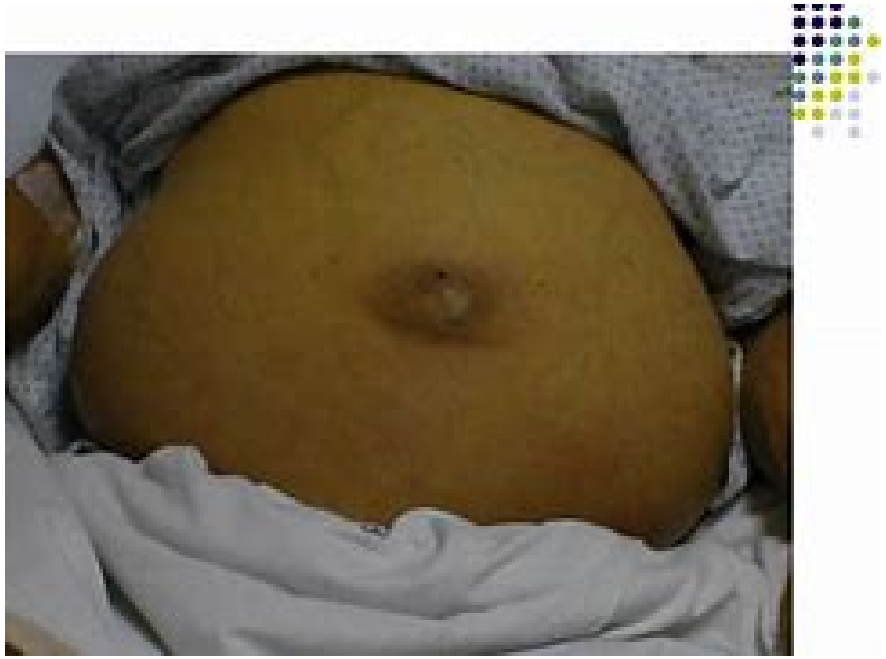
Skin and extrimities: Jaundice, flushing or pallor, palmar erythema, spider angiomata, digital clubbing, terry nails

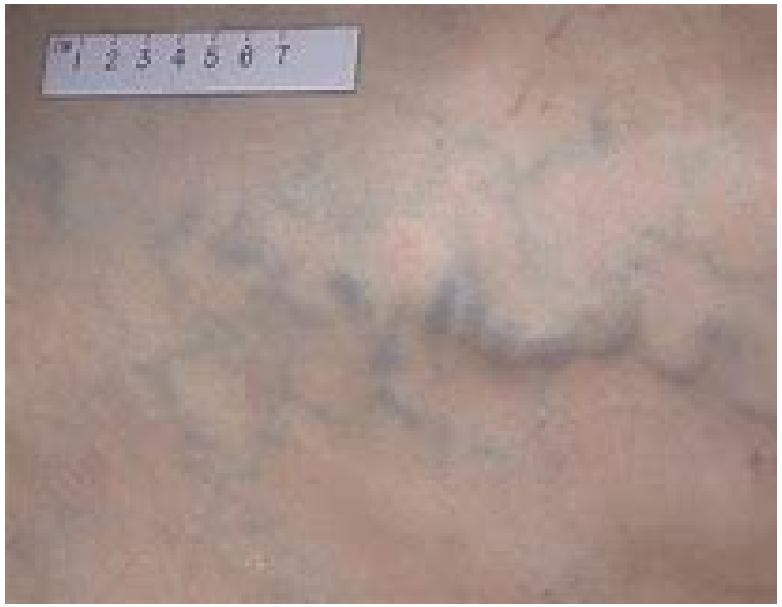






Abdomen: Distention, caput medusa, ascites, shrunken liver, large spleen, rectal varices





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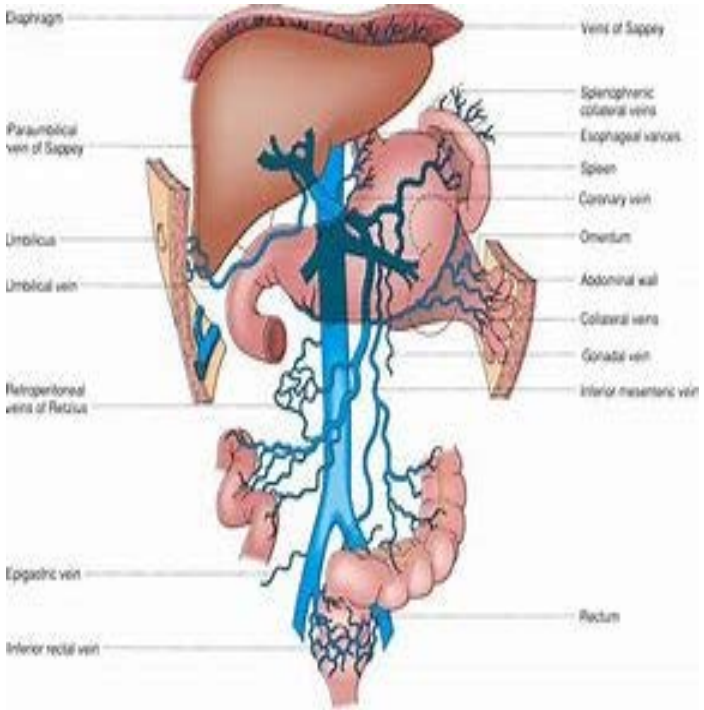
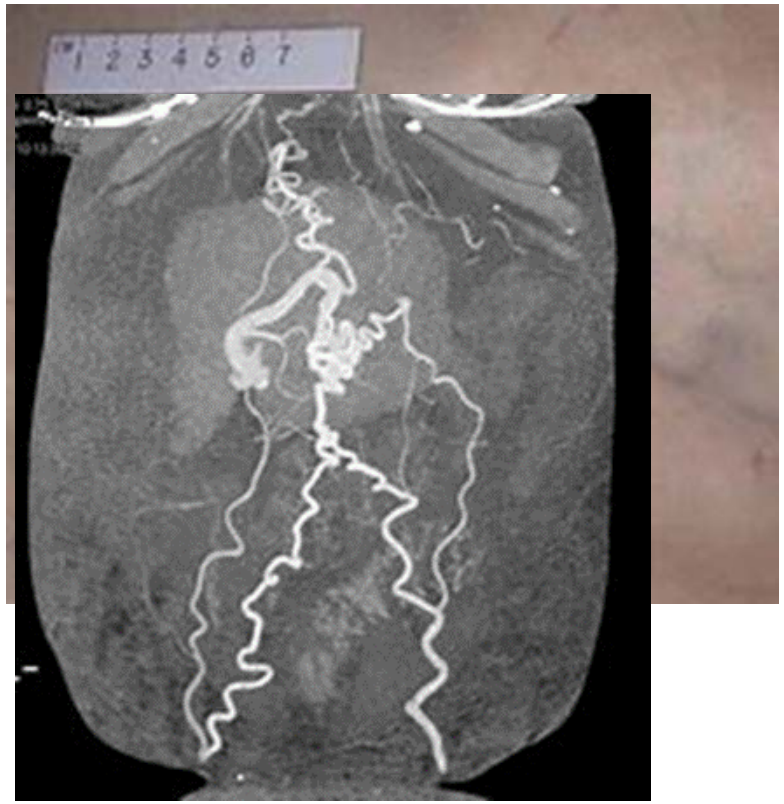
Collaterals in cirrhosis





Lab. Tests

- General tests to hematological, renal, pancreatic, and electrolyte abnormalities
- Liver-specific tests to assess the degree of

1. Inflammation
2. Injury
3. Function

- Dignostic tests

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Complications/Hematologic

- **PT and INR:**

1. To assess the severity of liver injury
2. But no the risk of bleeding
3. Because of balanced reduction in the pro(Factors 5, 7, 10, fibrinogen)
4. and anticoagulant proteins(Pr.C, S, antithrombin)
5. Infrequency of clinically important bleeding in ALF in the absence of *provocative* event such as infection and portal HTN is
6. So FFP transfusion or recombinant factor 7 should occur primarily in the setting of active bleeding or before invasive surgical procedure
7. Iv infusion of vit. K

- **Aplastic anemia**

1. Bone marrow failure => mild pancytopenia to aplastic anemia
2. Is identified most commonly in the setting of indeterminate ALF
3. Maye not be clinically evident until after emergency liver transplantation
4. Tx = immunomodulatory medications:

❖CS

Complications/ GI Tract

- **Ascites**

1. Some but not all patients
2. Precipitating factors:

↓Alb, ↑fluid administration, infection

Tx:

1. Fluid restriction
2. Diuretic should be reserved for patients with:

❖ Respiratory compromised

❖ Generalized fluid overload

(Overy aggressive diuresis => Hepatorenal syndrome

- **Bleeding**

1. Prophylactic acid reducing agents is often initiated but their usefulness is difficult to assess.

1. Causes:

- **Gastric erosions/ulcers (due to CS or idiopathic G/DU)**
- **Infection (So B/C and AB should be considered when GIB develops)**

2. Transfusion of PLT, PC, and FFP: If GIB is hemodynamically significant.

- **Pancreatitis**

1. **Is associated with multisystem failure in critically ill children.**
2. **Glucose and fluid management is more significant.**

Complications/Renal system

1. Renal insufficiency (because of medication or toxin)
2. Prerenal azotemia(Secondary to excessive fluid restriction, systemic hypotension in sepsis or hemorrhage)
3. Hepatorenal syndrome (in chronic liver diseases)
4. Simultaneously renal failure and ALF in toxic injury(acetaminophen, solvent, drugs)

HRS (Hepato Renal Syndrome)

Splancnic vasodilation → decrease effective blood volume →(+)R-A-A →

- Decrease renal perfusion
- AldI → Na retention

- Oliguria [UO<1cc/kg/h]
- U.Na<10
- FENa<1%
- U.Cr/Serum.Cr<10 [U:P Cr ratio]
- Normal U.Sedimentation
- No hypovolemia
- R/O other renal pathologies

Complications/Metabolic disorders

- **Hypoglycemia**

1. ↓Gluconeogenesis, ↓glycogen stores
2. Glucose infusion rate as high as 10-15 mg/kg/min may be required.

[cc/kg ×% Dextrose] ÷ 144 = mg/kg/min

- **Hypokalemia**

1. **Dilutional**
2. **Ascites**
3. **Renal wasting**

- **Hypophosphatemia**

Serum phosphor should be monitored frequently.

- **Acid-base disturbances**

1. **Hyperventilation=> resp.alk**
2. **Respiratory failure=> resp.acidosis**
3. **Hypokalemia=> met.alk**
4. **Hepatic necrosis, anaerobic metabolism, shock=> met.acidosis**

Complications/Infections

1. Enhanced susceptibility to bacterial infection and sepsis from immune dysfunction.
2. Evidence of infection may be subtle (tachycardia, intestinal bleeding, ↓renal output, changes in mental status)
3. Fever may not be present
4. Any evidence in clinical deterioration = Obtain B/C and initiation AB

Complications/Cardiopulmonary system

- Pulmonary edema(Secondary to *excessive fluid* administration)
- **Protection**:

1. Careful fluid restriction + discrete use of diuretics but with caution
2. CVP monitoring
3. Ionotropic support

Complications/ CNS[HE]

- A neuropsychiatric syndrome associated with hepatic dysfunction.
- Change in:

1. Behavior
2. Cognition
3. Neurologic examination
4. EEG

- **HE is not always clinically apparent in infants and young children.**
- **Distinguishing hepatic-based encephalopathy from other causes of an altered mental status such as :**
- **Sepsis**
- **Hypotension**
- **Electrolyte disturbances**
- **Anxiety**
- **ICU psychosis**

is difficult for all age groups

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- **Hyperammonemia play a central role in the development of HE in most cases**

Stages of HE (Clinical)

0 --- Non

I --- Infant/Child: *Inconsolable crying*, Inattention to task, Not acting like self to parents

Adult: Confused, *Mood* changes, *Altered sleep habits*, Forgetful

II --- Infant/Child: Like Stage I

Adult: *Drowsy*, inappropriate behavior, decreased inhibition

III --- Infant/Child:Somnolence, *stupor*, combativeness

Adult: *Stuporous*, obey simple commands

IV --- Infant/Child/Adult: *Comatose*, arouses with painful stimuli (IVa) or no response (IVb)

Stages of HE (DTR)

Infant/Child:

Normal --- Normal or hyper --- Normal or hyper --- Hyper --- Absent

0 I II III IV

Adult:

Normal --- Normal --- Hyper --- Hyper, Babinski(+) --- Absent

0 I II III IV

Stages of HE (Neurologic Signs)

Infant/Child:

Difficult or impossible to test adequately

I, II, III

Adult:

Tremor, Apraxia, Impaired hand-writing --- Dysarthria, ataxia --- Rigidity

I II III

In all age group:

***0: Non**

***IV: Decerebrate/decorticate**

Stages of HE (EEG)

Infant/Child:

Difficult or impossible to test adequately

I, II, III

Adult:

NL/diffuse slowing(θ)/triphasic w.--- AbNL/generalized slowing/triphasic w.

I **II, III**

In all age group:

***0:NL**

***IV: AbNL/very slow/Δ activity (Δ=4)**

نکات بالینی مراحل انسفالوپاتی کبدی

۱. در مرحله ۰ هیچ اتفاقی نیفتاده. (در همه گروههای سنی)
۲. در مرحله ۴ پاسخ به صدا نداشته. پس می رویم سراغ تحریک دردناک. بر اساس پاسخ یا عدم پاسخ به دو دسته آ و ب تقسیم میشود.
۳. در شیرخوار و کودک ۱و ۲ یکسانند.
۴. در بالغین خوابیدن در روز و بیداری در شب = ورود به مرحله ۱ انسفالوپاتی کبدی، یا یک تغییر خلق و حتی فراموشی یا گیجی.
۵. اما مرحله ۲ در بالغین آنست که کلا خواب آلود شده باشد، یا رفتارهای بی تناسب/ مهار گسیخته به هم زده باشد.
۶. هر کلمه ای درعلایم بالینی با « اس» شرع شود محله ۳ است:
Somnolence, Stupor, Simple commands (obey)

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Initial treatment of HE

- Minimising excess ***stimulation***
- Reducing ***protein intake***
- Treating ***suspected sepsis***
- Removing ***sedative*** medications
- ***Lactulose***(empirically); but lacks evidence of efficacy.
- Bowel "decontamination" with ***Rifaximin*** or ***Neomycin*** (as a second-tier treatment)
- Sodium benzoate (in ddults with cirrhosis)

[↑ICP is seen in HE, but no in all patients]

- ***Direct ICP monitoring*** **is the most sensitive and specific test compared with brain CT, but has more complications .**

[Generalized/focal seizures may occur in ALF that can be convulsive or non-convulsive]

- **In most cases *Phenytoin is initial treatment*.**
- **But in refractory seizures our optins will be Midazolam infusion, PB, Levetiracetam or Topiramate**

Complications/CNS[Brain edema]

- Is life threatening
- Occurs most commonly in cases with stage 3-4 HE
- Can be rapidly progressive
- The most sensitive test requires surgical placement of an ICP monitor.(But is high risk for the patient with an uncorrectable coagulopathy with a risk of bleeding between 10-20%.Activated factor VII has mde placement of monitors safer.

Pathogenesis of cerebral edema:

- Intraction among ammonia, cerebral blood flow, and inflammation.
- Ammonia enters the astrocytes [containing glutamine synthetase]
- Ammonia and glutamate → glutamine [A potent intracellular osmolyte] → Astrocyte swelling → Cerebral edema →Intracranial HTN.

- **Inflammatory milieu**
- **Sepsis**
- **Fluid/blood product administration**

<u>Can result in a sudden increased ICP</u>

Management of IC.HTN

- Maintain O2Sat>95%
- Fluid restriction [85-90% Maint]
- Diastolic pressure>40mmHg
- Adecuate sedation
- Empiric AB

- Haed elevation of 20 to 30 ° and nutral head position
- Hypertonic saline [goul: Na between 145-150meq/L]
- Monitol [Serum osm < 320mosm/L]
- Hypothermia [in adults has been used]

Nutrition
Avoid a catabolic state

- **Protein:**

1. 1 gr/kg/day (at least)
2. Adjustment may be needed based on *serum ammonia*

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- **Micronutrients:**

1. In liver disease: ↓Cu and Mn
2. In renal disease: ↓Cr, Mb, Selenium

- هر انسانی حق دارد به رسالتش شک کند و گاه آن را رها کند ، اما هرگز نباید رسالتش را فراموش کند.

پائولو کوئیلو