



# Liver Failure for the Hospitalist

## ACP Puerto Rico Chapter Meeting

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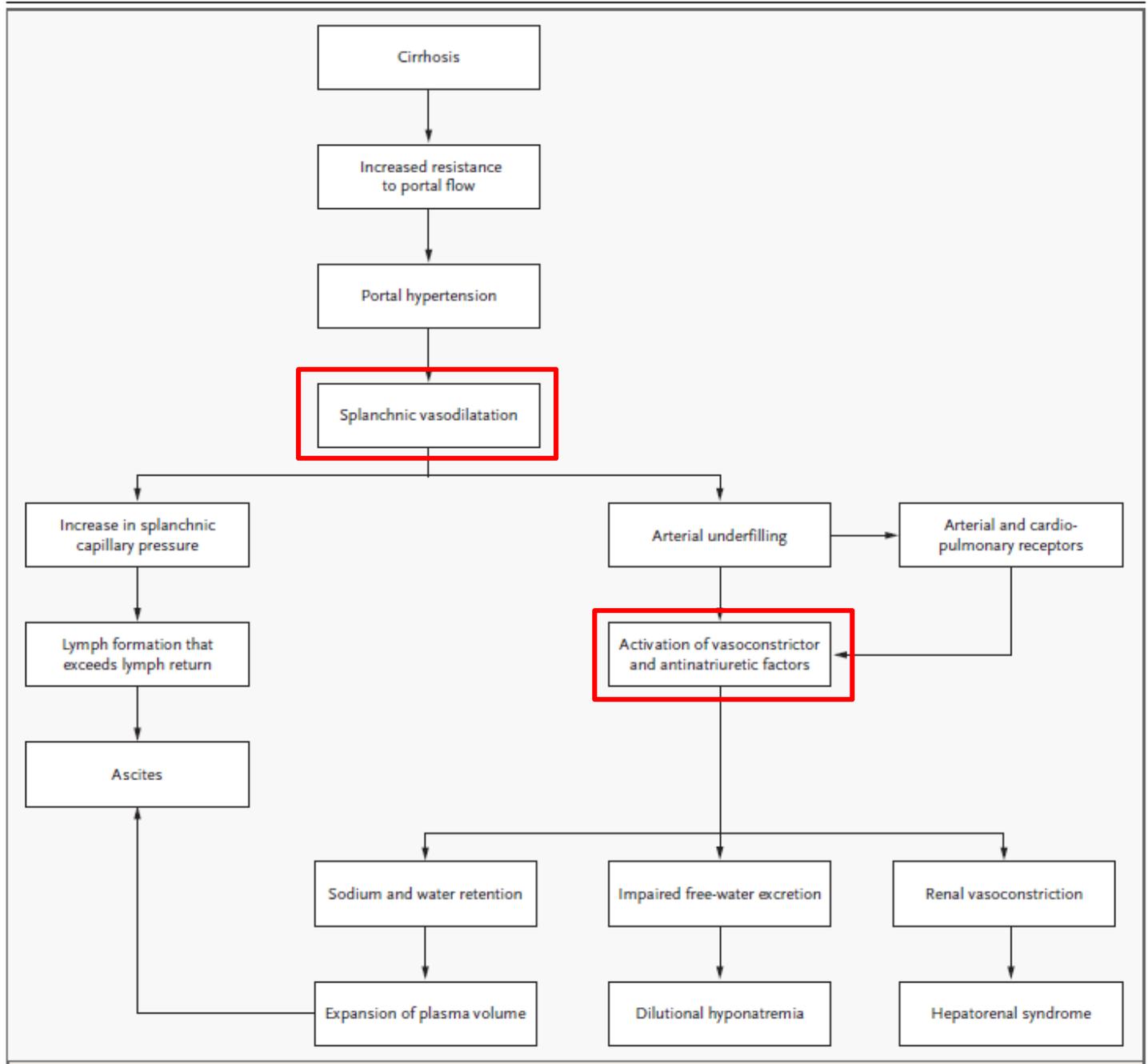
# Evolution of cirrhosis

## Compensated cirrhosis

- No complications
- Median survival > 12 years

## Decompensated cirrhosis

- Ascites, jaundice, hepatic encephalopathy, variceal bleeding or hepatocellular cancer
- Rate of 5-7% per year
- Median survival 2 years



# Hepatorenal syndrome

## Diagnosis

1. Cirrhosis with ascites
2. Diagnosis of acute kidney injury according to the revised criteria
3. No improvement in serum creatinine after at least 2 days of stopping diuretics and volume expansion with albumin at a dose of 1 g/kg body weight up to a maximum of 100 g per day
4. Absence of shock
5. No current or recent treatment with nephrotoxic drugs
6. Absence of parenchymal kidney disease as indicated by absence of proteinuria (>500 mg/day), microhematuria (>50 red blood cells/hpf) or abnormal renal ultrasound

# Revised criteria for diagnosis of acute kidney injury in patients with cirrhosis

**Table 2. International Club of Ascites (ICA-AKI) new definitions for the diagnosis and management of AKI in patients with cirrhosis.**

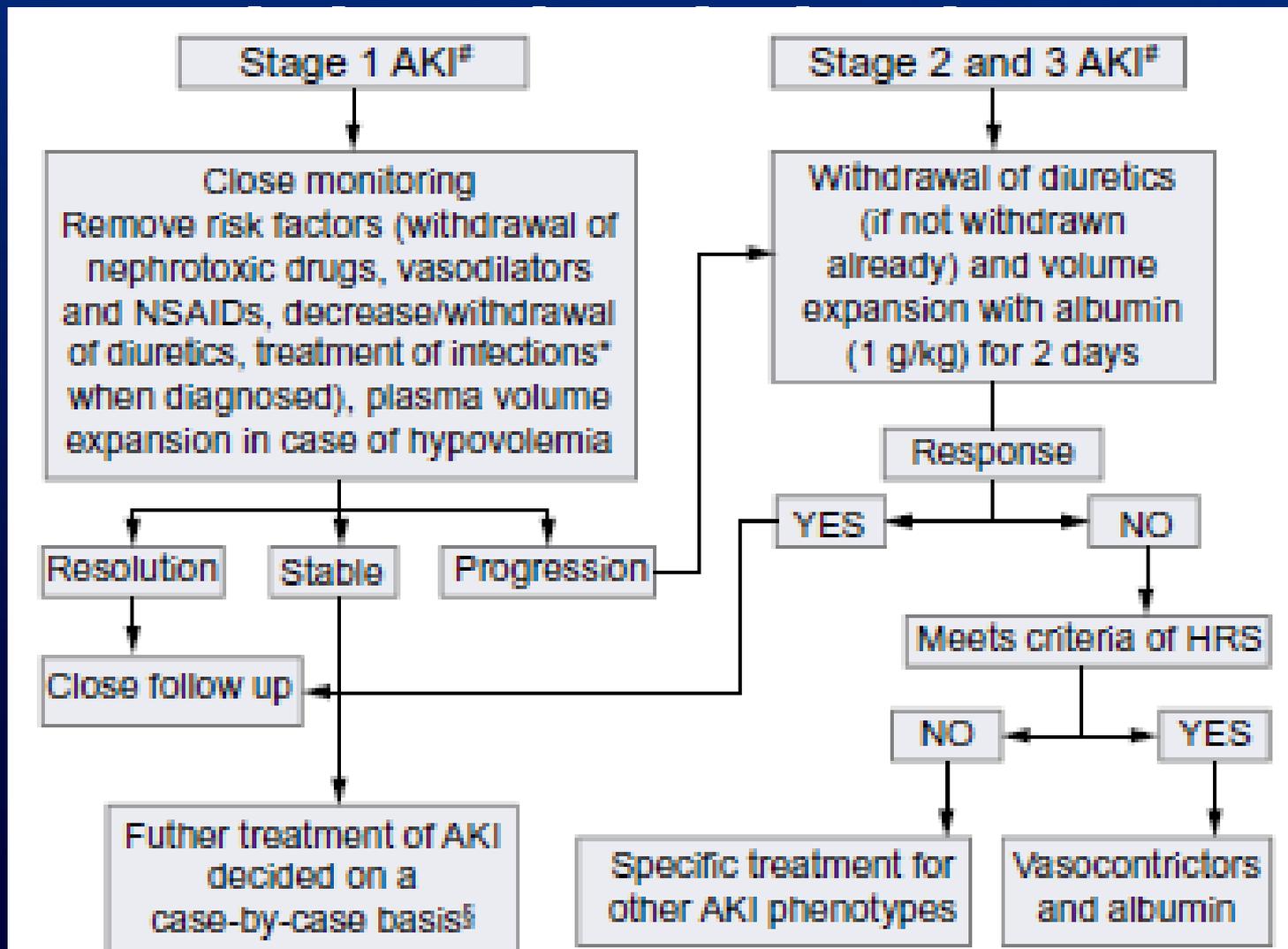
Subject	Definition		
Baseline sCr	A value of sCr obtained in the previous 3 months, when available, can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used. In patients without a previous sCr value, the sCr on admission should be used as baseline.		
Definition of AKI	<ul style="list-style-type: none"> <li>• Increase in sCr <math>\geq 0.3</math> mg/dl (<math>\geq 26.5</math> <math>\mu\text{mol/L}</math>) within 48 hours; or,</li> <li>• A percentage increase sCr <math>\geq 50\%</math> from baseline which is known, or presumed, to have occurred within the prior 7 days</li> </ul>		
Staging of AKI	<ul style="list-style-type: none"> <li>• <b>Stage 1:</b> increase in sCr <math>\geq 0.3</math> mg/dl (26.5 <math>\mu\text{mol/L}</math>) or an increase in sCr <math>\geq 1.5</math>-fold to 2-fold from baseline</li> <li>• <b>Stage 2:</b> increase in sCr <math>&gt;2</math>-fold to 3-fold from baseline</li> <li>• <b>Stage 3:</b> increase of sCr <math>&gt;3</math>-fold from baseline or sCr <math>\geq 4.0</math> mg/dl (353.6 <math>\mu\text{mol/L}</math>) with an acute increase <math>\geq 0.3</math> mg/dl (26.5 <math>\mu\text{mol/L}</math>) or initiation of renal replacement therapy</li> </ul>		
Progression of AKI	<b>Progression</b> Progression of AKI to a higher stage and/or need for RRT	<b>Regression</b> Regression of AKI to a lower stage	
Response to treatment	<b>No response</b> No regression of AKI	<b>Partial response</b> Regression of AKI stage with a reduction of sCr to $\geq 0.3$ mg/dl (26.5 $\mu\text{mol/L}$ ) above the baseline value	<b>Full response</b> Return of sCr to a value within 0.3 mg/dl (26.5 $\mu\text{mol/L}$ ) of the baseline value

AKI, acute kidney injury; RRT, renal replacement therapy; sCr, serum creatinine.

# Why serum creatinine not a good marker of renal function in cirrhotics

1. Decreased synthesis of creatinine from creatinine in muscles because of muscle wasting
2. Increased renal tubular secretion of creatinine
3. Increased volume of distribution in cirrhosis may dilute serum creatinine
4. Interference with assays of serum creatinine by elevated bilirubin

# New algorithm for management of acute kidney



# Hepatic encephalopathy

- It is a brain dysfunction caused by liver insufficiency or portal systemic shunting.
- One episode of hepatic encephalopathy is associated with 40% risk of another episode within the next 6 months
- Cirrhotics with mild cognitive dysfunction develop at least 1 bout of overt hepatic encephalopathy every 3 years of survival
- After TIPS the median 1 year incidence of overt hepatic encephalopathy is between 10-50%

# Clinical Features of HE

- In minimal hepatic encephalopathy attention, psychomotor speed and working memory are affected
- As it progresses personality changes such as irritability, disinhibition and irritability may be reported by the patient's relatives
- Disturbance of sleep wake cycle with excessive daytime sleepiness is frequent
- Progressive disorientation to time and space, inappropriate behavior, acute confusion with agitation or somnolence stupor and finally coma develops

# Clinical Features of HE

- Motor system abnormalities like hypertonia, hyper reflexia and positive Babinski sign are observed in non-comatose patient
- Extraparamidal dysfunction such as muscle rigidity, bradykinesia and Parkinson like tremor can occur
- Asterixis is a negative myoclonus due to loss of postural tone. It is best elicited by hyperextension of the wrist with separated fingers or rhythmic squeezing of the examiner's fingers.

# Factors precipitating HE

1. Infections
2. GI bleeding
3. Diuretic over does
4. Electrolyte disorders
5. Constipation

# Diagnosis of HE

- Lab testing: High blood ammonia alone does not help in HE patient with chronic liver disease. But if the ammonia level is normal then the diagnosis of HE could be questioned
- Brain scans have limited utility in the absence of localizing neurologic signs. Main differential is intracranial hemorrhage

# Management of HE

Four steps to managing HE

1. Initiate care for patients with altered consciousness
2. Find alternative causes for altered mental status and treat them
3. Identify precipitating factors and treat them nearly 90% patient and treated by just treating the precipitating factor
4. Commence empirical treatment of hepatic encephalopathy

# Management of HE

## Lactulose

1. Nonabsorbable disaccharide
2. Start treatment with 25 ml of syrup every 1-2 hours until at least 2 soft or loose bowel movements are produced
3. Subsequently doses titrated to maintain 2-3 soft bowel movements per day
4. Over using lactulose can lead to aspiration, dehydration, hypernatremia and severe perianal irritation and can also precipitate hepatic encephalopathy

# Management of HE

## Rifaximin

- Effective add on therapy to lactulose to prevent recurrence of hepatic encephalopathy
- Neomycin and metronidazole are alternative antibiotics to treat hepatic encephalopathy but there is a risk of oto or nephrotoxicity with both and neurotoxicity with metronidazole

hepatic encephalopathy after TIPS

This does not respond to lactulose or rifaximin.

Treatment is narrowing of the TIPS shunt

# Management of HE

## **Hepatic encephalopathy after TIPS**

This does not respond to lactulose or rifaximin.  
Treatment is narrowing of the tips shunt

## **Hepatic encephalopathy after spontaneous portal systemic shunt such as splenorenal shunt**

Managed by embolization of these shunt with rapid clearance of hepatic encephalopathy. The risk is subsequent variceal bleeding

# Nutrition in HE

- Nearly 75% of patients with hepatic encephalopathy suffer from moderate to severe protein calorie malnutrition with loss of muscle mass and energy reserves
- Chronic protein restriction is detrimental because these patients have greater protein requirements
- Sarcopenia is an important negative prognostic factor in cirrhotics

# Nutrition in HE

- Daily energy intake should be 35-40 kilocalories per kg ideal body weight
- Daily protein intake should be 1.2-1.5 per day

# Acute Liver Failure

- Rapid deterioration of liver dysfunction manifesting as coagulopathy (INR $\geq$ 1.5)
- Any degree of altered mental status
- Illness of <26 weeks duration
- In someone with no known history of chronic liver disease

**Exceptions** (ALF diagnosed even in presence of underlying cirrhosis if their disease was recognized <26 weeks back)

- Wilsons disease
- Vertically transmitted Hepatitis B
- Autoimmune hepatitis

# Diagnosis and Initial Evaluation

Acute hepatitis



Prothrombin  
time



Prolonged by 4-6 seconds or INR  $\geq$   
1.5 plus any degree of altered  
mental status



Transfer to ICU  
Contact transplant center

# Etiology and Specific Therapies

## Acetaminophen toxicity

- Dose related- most ingestions leading to ALF exceed 10 gm/d (150 mg/kg) but can occur with as low as 3-4 g/d
- Clues: very high aminotransferases (>3,500 IU/L) with low bilirubin in the absence of hypotension

# Etiology and Specific Therapies

## Acetaminophen toxicity

### Management:

- Activated charcoal effective if given upto 4 hours usually through NG tube
- N-acetylcysteine is specific antidote- effective for upto 48 hours- begin IV if acetaminophen toxicity is suspected continue for at least 72 hrs or until liver chemistries improve
- Drug levels may be low or undetectable if ingestion was remote or over period of time

# Etiology and Specific Therapies

## **Amanita phalloides poisoning**

- Diagnosis made by history- severe GI symptoms (nausea, vomiting, abdominal cramping diarrhea) within hours to one day of ingesting mushrooms
- No blood test available to confirm presence of toxins
- Gastric lavage and activated charcoal via NG tube may help if identified early

# Etiology and Specific Therapies

## **Amanita phalloides poisoning**

- Specific antidotes: Penicillin G and silibinin (silymarin or milk thistle) – no controlled trials of their efficacy
- Dose: Penicillin G 300,000 to 1 million Units/kg/d
- Silibinin is not available as a licensed drug in the United States
- NAC is often combined with these therapies but not effective in animal studies

Often poor survival without liver transplantation

# Etiology and Specific Therapies

## Drug induced liver injury

- Most cases of idiosyncratic drug hepatotoxicity occur within 6 months after drug initiation
- A potentially hepatotoxic medication used continually for more than 1-2 years is unlikely to cause de novo liver damage
- Common classes of drugs implicated
  - Antibiotics
  - NSAIDs
  - Antiepileptics
  - Herbals
  - Weight loss agents
  - Nutritional Supplements

# Etiology and Specific Therapies

Isoniazid	Pyrazinamide
Sulfasalazine	Isoflurane
Phenytoin	Itraconazole
Statins	Nicotinic acid
Propylthiouracil	Imipramine
Ciprofloxacin	Gemtuzumab
Nitrofurantoin	Terbinafine
Disulfiram	Methyldopa
Cocaine	MDMA (Ecstasy)
Valproic acid	Labetalol
Amiodarone	Tolcapone
Dapsone	Allopurinol
Etodolac	Methyldopa
Didanosine	Ketoconazole
Efavirenz	Abacavir
Carbamazepine	Doxycycline
Valproic Acid	Diclofenac

#### Combination agents with enhanced toxicity:

Trimethoprim-sulfamethoxazole  
Rifampin-Isoniazid  
Amoxicillin-clavulanate

#### Some herbal products/dietary supplements that have been associated with hepatotoxicity include:

Kava Kava	Greater celandine
Herbalife	He Shon Wu
Hydroxycut	LipoKinetix
Comfrey	Ma Huang
Senecio	

## Take home points

- Obtain details (onset of ingestion, amount and timing of last dose) of all prescription and non-prescription drugs, herbs and dietary supplements taken over the past year
- Determine ingredients of non-prescription medications whenever possible

# Etiology and Specific Therapies

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Nitrofurantoin	Terbinafine
Disulfiram	Methyldopa
Cocaine	MDMA (Ecstasy)
Valproic acid	Labetalol
Amiodarone	Tolcapone
Dapsone	Allopurinol
Etodolac	Methyldopa
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## Take home points

- In the setting of acute liver failure due to possible drug hepatotoxicity, discontinue all but essential medications
- N-acetylcysteine may be beneficial for acute liver failure due to drug-induced liver injury

# Etiology and Specific Therapies

## Viral Hepatitis

- Relatively infrequent in US (12% overall, 8% hepatitis B, 4% hepatitis A)
- Hepatitis serologies should be tested even if another putative etiology is identified
- Acute hepatitis D may be diagnosed in a hepatitis B positive individual
- Hepatitis E can cause liver failure in endemic areas (Consider in recent travelers to India, Pakistan, Mexico, Russia), particularly in pregnant women

# Etiology and Specific Therapies

## Viral Hepatitis

- ALF may occur due to reactivation of chronic hepatitis B in someone receiving chemotherapy or immunosuppression- so all these patients should have HbsAg checked before starting treatment.

## HSV

- Immunosuppressed patients, pregnant women are at increased risk. Test with HSV IgM+HSV DNA
- Skin lesions may be absent
- Usually anicteric and septic
- Treatment with acyclovir
- Refer for transplant

# Etiology and Specific Therapies

## Wilson disease

- Rare (2-3% of US cases)
- ALF due to Wilson disease is 100% fatal without liver transplant
- Typically occurs in young patients (<40 years old) manifesting as coombs negative hemolytic anemia with marked hyperbilirubinemia (>20 mg/dl)
- Kayser Fleischer rings present in 50% patients presenting with ALF

# Etiology and Specific Therapies

## Wilson disease

- Serum ceruloplasmin level may be normal in 15% patients at presentation, low in 50% of non-Wilson disease patients with ALF
- Elevated urine copper and hepatic copper measurement confirms the diagnosis
- Very low alkaline phosphatase or serum uric acid and high bilirubin to alkaline phosphatase ratio ( $>2$ ) suggest of Wilson disease
- Penicillamine is not recommended in ALF due to risk of hypersensitivity

# Etiology and Specific Therapies

## Take home points

- To exclude Wilson disease obtain ceruloplasmin, serum and urinary copper levels, slit lamp examination for Kayser-Fleischer rings, hepatic copper levels when liver biopsy is feasible, and total bilirubin/alkaline phosphatase ratio
- Patients in whom Wilson disease is the likely cause of acute liver failure must be promptly considered for liver transplantation

# Etiology and Specific Therapies

## Autoimmune hepatitis

- Liver biopsy is recommended when autoimmune hepatitis is suspected as the cause of acute liver failure, and autoantibodies are negative
- Corticosteroids (prednisone 40-60 mg/d) may be given to patients who have coagulopathy and mild hepatic encephalopathy

# Etiology and Specific Therapies

## Acute fatty liver of pregnancy/ HELLP syndrome

- Occurs in third trimester
- Jaundice, coagulopathy and thrombocytopenia may be associated with hypoglycemia
- Expeditious delivery of the infant is critical for good outcome
- Recovery is typically rapid after delivery, and usually supportive care is the only treatment required

# Etiology and Specific Therapies

## Acute ischemic hepatitis or shock liver

- Usually precipitated by cardiac arrest or any period of significant hypotension or in severe congestive heart failure
- Drug induced hypoperfusion may occur with long acting niacin, cocaine or methamphetamine
- Aminotransferases are markedly elevated
- Simultaneous onset of renal dysfunction and muscle necrosis may be noted
- Recovery is rapid but long term outcome depends on the underlying cardiac process
- Treatment: cardiovascular support

# Etiology and Specific Therapies

## **Budd Chiari syndrome (acute hepatic vein thrombosis)**

- Triad of abdominal pain, ascites and striking hepatomegaly
- Doppler ultrasound or MR venography will identify the clot
- Test for hypercoagulable conditions (polycythemia, cancer)
- If ALF is present, prognosis is poor without liver transplant

# Etiology and Specific Therapies

## Indeterminate etiology

- Transjugular liver biopsy may help diagnose infiltrating cancer, autoimmune hepatitis, certain viral infections and Wilson disease
- Most cases subsequently turn out to be acetaminophen, autoimmune hepatitis and cancer

# Intensive Care of Acute Liver Failure

## Grades of encephalopathy

GRADE	DEFINITION
I	Changes in behavior with minimal change in level of consciousness
II	Gross disorientation, drowsiness, possibly asterixis, inappropriate behavior
III	Marked confusion; incoherent speech, sleeping most of the time but arousable to vocal stimuli
IV	Comatose, unresponsive to pain, decorticate or decerebrate posturing

*Note: some patients will overlap grades; clinical judgment is required. Adapted from Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, Levy LL. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. Gastroenterology 1977;72:573-583.*

# Intensive Care of Acute Liver Failure

## Cerebral Edema/Intracranial Hypertension

### Grade I/II Encephalopathy

Consider transfer to liver transplant facility and listing for transplantation

Brain CT: rule out other causes of decreased mental status; little utility to identify cerebral edema

Avoid stimulation; avoid sedation if possible

Antibiotics: surveillance and treatment of infection required; prophylaxis possibly helpful

Lactulose, possibly helpful

### Grade III/IV Encephalopathy

Continue management strategies listed above

Intubate trachea (may require sedation)

Elevate head of bed

Consider placement of ICP monitoring device

Immediate treatment of seizures required; prophylaxis of unclear value

Mannitol: use for severe elevation of ICP or first clinical signs of herniation

Hypertonic saline to raise serum sodium to 145-155 mmol/L

Hyperventilation: effects short-lived; may use for impending herniation

# Intensive Care of Acute Liver Failure

## Coagulopathy

Vitamin K: give at least one dose

FFP: give only for invasive procedures or active bleeding

Platelets: give only for invasive procedures or active bleeding

Recombinant activated factor VII: possibly effective for invasive procedures

Prophylaxis for stress ulceration: give H<sub>2</sub> blocker or PPI

## Hemodynamics/Renal Failure

Volume replacement

Pressor support (dopamine, epinephrine, norepinephrine) as needed to maintain adequate mean arterial pressure

Avoid nephrotoxic agents

Continuous modes of hemodialysis if needed

Vasopressin recommended in hypotension refractory to volume resuscitation and no repinephrine

## Metabolic Concerns

Follow closely: glucose, potassium, magnesium, phosphate

Consider nutrition: enteral feedings if possible or total parenteral nutrition

# Central Nervous System effects of Acute Liver Failure

- Cerebral edema and raised intra cranial tension are the most serious complications of ALF
- Pathogenesis unclear- osmotic disturbances in the brain and increased cerebral blood flow due to loss of autoregulation, inflammation or infection
- Increases with worsening encephalopathy (upto 75% in grade IV)

# Central Nervous System effects of Acute Liver Failure

- Grade 1 encephalopathy may be safely managed in a quiet ward with skilled nursing
- Grade 2 or higher encephalopathy should be managed in the ICU
- Sedation is avoided. Unmanageable agitation may be treated with short-acting benzodiazepines in small doses
- Grade III or IV encephalopathy warrants mechanical ventilation
- Propofol is the sedative of choice as it may decrease cerebral blood flow.

# Central Nervous System effects of Acute Liver Failure

## Lactulose

- Arterial ammonia  $> 200$  mg/dl is strongly associated with cerebral herniation
- A study comparing ALF patients who received lactulose to those who did not found a small increase in survival time in those receiving lactulose without difference in overall outcome
- Gaseous distension of bowel from lactulose may cause technical difficulties during liver transplantation

# Central Nervous System effects of Acute Liver Failure

## Seizures

- Phenytoin is suggested as first line drug
- Short acting benzodiazepines suggested in phenytoin refractory cases

# Intra cranial hypertension

- Intra cranial pressure (ICP) monitoring allows assessment of cerebral perfusion pressure (mean arterial pressure- intra cranial pressure)
- Goal is to maintain ICP < 20 mm Hg and CPP > 60 mm Hg by giving osmotically active agents or vasopressors
- Risks of ICP monitors- bleeding and infection

# Intra cranial hypertension

## Treatment of raised ICP

- Increase plasma volume with IV fluids and then vasopressors
- CRRT in renal failure patients to remove about 500 ml plasma volume
- IV mannitol transiently decreases ICP – recommended as 1<sup>st</sup> line therapy if ICH develops
- Risks of mannitol- volume overload, hyperosmolarity and hypernatremia
- Hyperventilation to a PaCO<sub>2</sub> of 25-30 mm Hg restores cerebral autoregulation, vasoconstriction and reduces ICP- delays cerebral herniation.

# Intra cranial hypertension

## Treatment of raised ICP

- Patients at highest risk of cerebral edema (high serum ammonia, high grade hepatic encephalopathy, acute renal failure or on pressors) can be treated prophylactically with hypertonic saline (goal serum sodium 145-155 mEQ/L)
- Corticosteroids have no role in managing cerebral edema in ALF

# Infections

ALF patients are at high risk for infections

- Periodic surveillance cultures are recommended to detect bacterial and fungal pathogens. Antibiotic treatment should be initiated promptly according to surveillance culture results at the earliest sign of active infection or deterioration (progression to high grade hepatic encephalopathy or elements of the SIRS)
- Prophylactic antibiotics and antifungals have not been shown to improve overall outcomes and are therefore not recommended

# Coagulopathy

- Although INR is elevated, in absence of bleeding correction of INR is not advisable as trends in INR are prognostic
- Vitamin K (5-10 mg SQ) should be administered routinely as deficiency has been reported in ALF
- If there is clinically significant bleeding or in anticipation of a high risk procedure, treatment with recombinant factor VII (if available) may be considered.

# Coagulopathy

- Platelets are recommended if there is spontaneous bleeding or prior to invasive procedures or if platelet count is  $< 10,000/\text{mm}^3$
- For invasive procedures, platelet count of 50,000-70,000/ $\text{mm}^3$  is adequate
- Prophylaxis with H2 blockers or PPIs (sucralfate is 2<sup>nd</sup> line) is recommended in ALF patients in the ICU to prevent GI bleeding associated with stress

# Hemodynamics

- Low systemic vascular resistance is the fundamental hemodynamic abnormality in ALF
- Goal is to maintain MAP at least 75 mm Hg and CPP 60-80 mm Hg
- Most patients with ALF are dehydrated due to decreased oral intake and third spacing
- Normal saline is recommended fluid in dehydrated ALF patients. Should be changed to half-normal saline with 75 mEq/L sodium bicarbonate if patient becomes acidotic.
- Crystalloid solutions should contain dextrose to avoid hypoglycemia

# Hemodynamics

- Second line is inotropic support- norepinephrine is preferred 1<sup>st</sup> line
- Vasopressin can be added in patients who do not respond to IV fluids and norepinephrine
- Hydrocortisone can be tried if hypotension persists

# Metabolic concerns

- Hypoglycemia is managed with continuous glucose infusion
- Phosphate, magnesium and potassium are frequently low and require repeated supplementation
- Enteral feedings should be initiated early- 60 g of protein daily is reasonable in most patients
- If enteral feeds are contraindicated, parenteral nutrition should be considered- both these decrease risk of GI bleeding due to stress ulcers

# Prognostic models in Acute Liver Failure

Etiologies with good transplant free survival ( $\geq 50\%$ )

- Acetaminophen
- Hepatitis A
- Shock liver
- Pregnancy related liver disease

Currently available prognostic scoring systems do not adequately predict outcome and determine candidacy for liver transplantation. Reliance entirely upon these guidelines is thus not recommended.

# Hepatic encephalopathy

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Ciprofloxacin	Gemtuzumab
Nitrofurantoin	Terbinafine
Disulfiram	Methyldopa
Cocaine	MDMA (Ecstasy)
Valproic acid	Labetalol
Amiodarone	Tolcapone
Dapsone	Allopurinol
Etodolac	Methyldopa
Didanosine	Ketoconazole
Efavirenz	Abacavir
Carbamazepine	Doxycycline
Valproic Acid	Diclofenac

#### Combination agents with enhanced toxicity:

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Senecio	

## Take home points

- Obtain details (onset of ingestion, amount and timing of last dose) of all prescription and non-prescription drugs, herbs and dietary supplements taken over the past year
- Determine ingredients of non-prescription medications whenever possible

# Etiology and Specific Therapies

Isoniazid	Pyrazinamide
Sulfasalazine	Isoflurane
Phenytoin	Itraconazole
Statins	Nicotinic acid
Propylthiouracil	Imipramine
Ciprofloxacin	Gemtuzumab
Nitrofurantoin	Terbinafine
Disulfiram	Methyldopa
Cocaine	MDMA (Ecstasy)
Valproic acid	Labetalol
Amiodarone	Tolcapone
Dapsone	Allopurinol
Etodolac	Methyldopa
Didanosine	Ketoconazole
Efavirenz	Abacavir
Carbamazepine	Doxycycline
Valproic Acid	Diclofenac

#### Combination agents with enhanced toxicity:

Trimethoprim-sulfamethoxazole  
Rifampin-Isoniazid  
Amoxicillin-clavulanate

#### Some herbal products/dietary supplements that have been associated with hepatotoxicity include:

Kava Kava	Greater celandine
Herbalife	He Shon Wu
Hydroxycut	LipoKinetic
Comfrey	Ma Huang
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## Take home points

- In the setting of acute liver failure due to possible drug hepatotoxicity, discontinue all but essential medications
- N-acetylcysteine may be beneficial for acute liver failure due to drug-induced liver injury

# Etiology and Specific Therapies

## Viral Hepatitis

- Relatively infrequent in US (12% overall, 8% hepatitis B, 4% hepatitis A)
- Hepatitis serologies should be tested even if another putative etiology is identified
- Acute hepatitis D may be diagnosed in a hepatitis B positive individual
- Hepatitis E can cause liver failure in endemic areas (Consider in recent travelers to India, Pakistan, Mexico, Russia), particularly in pregnant women

# Etiology and Specific Therapies

## Viral Hepatitis

- ALF may occur due to reactivation of chronic hepatitis B in someone receiving chemotherapy or immunosuppression- so all these patients should have HbsAg checked before starting treatment.

## HSV

- Immunosuppressed patients, pregnant women are at increased risk. Test with HSV IgM+HSV DNA
- Skin lesions may be absent
- Usually anicteric and septic
- Treatment with acyclovir
- Refer for transplant

# Etiology and Specific Therapies

## Wilson disease

- Rare (2-3% of US cases)
- ALF due to Wilson disease is 100% fatal without liver transplant
- Typically occurs in young patients (<40 years old) manifesting as coombs negative hemolytic anemia with marked hyperbilirubinemia (>20 mg/dl)
- Kayser Fleischer rings present in 50% patients presenting with ALF

# Etiology and Specific Therapies

## Wilson disease

- Serum ceruloplasmin level may be normal in 15% patients at presentation, low in 50% of non-Wilson disease patients with ALF
- Elevated urine copper and hepatic copper measurement confirms the diagnosis
- Very low alkaline phosphatase or serum uric acid and high bilirubin to alkaline phosphatase ratio ( $>2$ ) suggest of Wilson disease
- Penicillamine is not recommended in ALF due to risk of hypersensitivity

# Etiology and Specific Therapies

## Take home points

- To exclude Wilson disease obtain ceruloplasmin, serum and urinary copper levels, slit lamp examination for Kayser-Fleischer rings, hepatic copper levels when liver biopsy is feasible, and total bilirubin/alkaline phosphatase ratio
- Patients in whom Wilson disease is the likely cause of acute liver failure must be promptly considered for liver transplantation

# Etiology and Specific Therapies

## Autoimmune hepatitis

- Liver biopsy is recommended when autoimmune hepatitis is suspected as the cause of acute liver failure, and autoantibodies are negative
- Corticosteroids (prednisone 40-60 mg/d) may be given to patients who have coagulopathy and mild hepatic encephalopathy

# Etiology and Specific Therapies

## Acute fatty liver of pregnancy/ HELLP syndrome

- Occurs in third trimester
- Jaundice, coagulopathy and thrombocytopenia may be associated with hypoglycemia
- Expeditious delivery of the infant is critical for good outcome
- Recovery is typically rapid after delivery, and usually supportive care is the only treatment required

# Etiology and Specific Therapies

## Acute ischemic hepatitis or shock liver

- Usually precipitated by cardiac arrest or any period of significant hypotension or in severe congestive heart failure
- Drug induced hypoperfusion may occur with long acting niacin, cocaine or methamphetamine
- Aminotransferases are markedly elevated
- Simultaneous onset of renal dysfunction and muscle necrosis may be noted
- Recovery is rapid but long term outcome depends on the underlying cardiac process
- Treatment: cardiovascular support

# Etiology and Specific Therapies

## **Budd Chiari syndrome (acute hepatic vein thrombosis)**

- Triad of abdominal pain, ascites and striking hepatomegaly
- Doppler ultrasound or MR venography will identify the clot
- Test for hypercoagulable conditions (polycythemia, cancer)
- If ALF is present, prognosis is poor without liver transplant

# Etiology and Specific Therapies

## Indeterminate etiology

- Transjugular liver biopsy may help diagnose infiltrating cancer, autoimmune hepatitis, certain viral infections and Wilson disease
- Most cases subsequently turn out to be acetaminophen, autoimmune hepatitis and cancer

# Intensive Care of Acute Liver Failure

## Grades of encephalopathy

GRADE	DEFINITION
I	Changes in behavior with minimal change in level of consciousness
II	Gross disorientation, drowsiness, possibly asterixis, inappropriate behavior
III	Marked confusion; incoherent speech, sleeping most of the time but arousable to vocal stimuli
IV	Comatose, unresponsive to pain, decorticate or decerebrate posturing

*Note: some patients will overlap grades; clinical judgment is required. Adapted from Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, Levy LL. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. Gastroenterology 1977;72:573-583.*

# Intensive Care of Acute Liver Failure

## Cerebral Edema/Intracranial Hypertension

### Grade I/II Encephalopathy

Consider transfer to liver transplant facility and listing for transplantation

Brain CT: rule out other causes of decreased mental status; little utility to identify cerebral edema

Avoid stimulation; avoid sedation if possible

Antibiotics: surveillance and treatment of infection required; prophylaxis possibly helpful

Lactulose, possibly helpful

### Grade III/IV Encephalopathy

Continue management strategies listed above

Intubate trachea (may require sedation)

Elevate head of bed

Consider placement of ICP monitoring device

Immediate treatment of seizures required; prophylaxis of unclear value

Mannitol: use for severe elevation of ICP or first clinical signs of herniation

Hypertonic saline to raise serum sodium to 145-155 mmol/L

Hyperventilation: effects short-lived; may use for impending herniation

# Intensive Care of Acute Liver Failure

## Coagulopathy

Vitamin K: give at least one dose

FFP: give only for invasive procedures or active bleeding

Platelets: give only for invasive procedures or active bleeding

Recombinant activated factor VII: possibly effective for invasive procedures

Prophylaxis for stress ulceration: give H<sub>2</sub> blocker or PPI

## Hemodynamics/Renal Failure

Volume replacement

Pressor support (dopamine, epinephrine, norepinephrine) as needed to maintain adequate mean arterial pressure

Avoid nephrotoxic agents

Continuous modes of hemodialysis if needed

Vasopressin recommended in hypotension refractory to volume resuscitation and no repinephrine

## Metabolic Concerns

Follow closely: glucose, potassium, magnesium, phosphate

Consider nutrition: enteral feedings if possible or total parenteral nutrition

# Central Nervous System effects of Acute Liver Failure

- Cerebral edema and raised intra cranial tension are the most serious complications of ALF
- Pathogenesis unclear- osmotic disturbances in the brain and increased cerebral blood flow due to loss of autoregulation, inflammation or infection
- Increases with worsening encephalopathy (upto 75% in grade IV)

# Central Nervous System effects of Acute Liver Failure

- Grade 1 encephalopathy may be safely managed in a quiet ward with skilled nursing
- Grade 2 or higher encephalopathy should be managed in the ICU
- Sedation is avoided. Unmanageable agitation may be treated with short-acting benzodiazepines in small doses
- Grade III or IV encephalopathy warrants mechanical ventilation
- Propofol is the sedative of choice as it may decrease cerebral blood flow.

# Central Nervous System effects of Acute Liver Failure

## Lactulose

- Arterial ammonia  $> 200$  mg/dl is strongly associated with cerebral herniation
- A study comparing ALF patients who received lactulose to those who did not found a small increase in survival time in those receiving lactulose without difference in overall outcome
- Gaseous distension of bowel from lactulose may cause technical difficulties during liver transplantation

# Central Nervous System effects of Acute Liver Failure

## Seizures

- Phenytoin is suggested as first line drug
- Short acting benzodiazepines suggested in phenytoin refractory cases

# Intra cranial hypertension

- Intra cranial pressure (ICP) monitoring allows assessment of cerebral perfusion pressure (mean arterial pressure- intra cranial pressure)
- Goal is to maintain ICP < 20 mm Hg and CPP > 60 mm Hg by giving osmotically active agents or vasopressors
- Risks of ICP monitors- bleeding and infection

# Intra cranial hypertension

## Treatment of raised ICP

- Increase plasma volume with IV fluids and then vasopressors
- CRRT in renal failure patients to remove about 500 ml plasma volume
- IV mannitol transiently decreases ICP – recommended as 1<sup>st</sup> line therapy if ICH develops
- Risks of mannitol- volume overload, hyperosmolarity and hypernatremia
- Hyperventilation to a PaCO<sub>2</sub> of 25-30 mm Hg restores cerebral autoregulation, vasoconstriction and reduces ICP- delays cerebral herniation.

# Intra cranial hypertension

## Treatment of raised ICP

- Patients at highest risk of cerebral edema (high serum ammonia, high grade hepatic encephalopathy, acute renal failure or on pressors) can be treated prophylactically with hypertonic saline (goal serum sodium 145-155 mEQ/L)
- Corticosteroids have no role in managing cerebral edema in ALF

# Infections

ALF patients are at high risk for infections

- Periodic surveillance cultures are recommended to detect bacterial and fungal pathogens. Antibiotic treatment should be initiated promptly according to surveillance culture results at the earliest sign of active infection or deterioration (progression to high grade hepatic encephalopathy or elements of the SIRS)
- Prophylactic antibiotics and antifungals have not been shown to improve overall outcomes and are therefore not recommended

# Coagulopathy

- Although INR is elevated, in absence of bleeding correction of INR is not advisable as trends in INR are prognostic
- Vitamin K (5-10 mg SQ) should be administered routinely as deficiency has been reported in ALF
- If there is clinically significant bleeding or in anticipation of a high risk procedure, treatment with recombinant factor VII (if available) may be considered.

# Coagulopathy

- Platelets are recommended if there is spontaneous bleeding or prior to invasive procedures or if platelet count is  $< 10,000/\text{mm}^3$
- For invasive procedures, platelet count of 50,000-70,000/ $\text{mm}^3$  is adequate
- Prophylaxis with H2 blockers or PPIs (sucralfate is 2<sup>nd</sup> line) is recommended in ALF patients in the ICU to prevent GI bleeding associated with stress

# Hemodynamics

- Low systemic vascular resistance is the fundamental hemodynamic abnormality in ALF
- Goal is to maintain MAP at least 75 mm Hg and CPP 60-80 mm Hg
- Most patients with ALF are dehydrated due to decreased oral intake and third spacing
- Normal saline is recommended fluid in dehydrated ALF patients. Should be changed to half-normal saline with 75 mEq/L sodium bicarbonate if patient becomes acidotic.
- Crystalloid solutions should contain dextrose to avoid hypoglycemia

# Hemodynamics

- Second line is inotropic support- norepinephrine is preferred 1<sup>st</sup> line
- Vasopressin can be added in patients who do not respond to IV fluids and norepinephrine
- Hydrocortisone can be tried if hypotension persists

# Metabolic concerns

- Hypoglycemia is managed with continuous glucose infusion
- Phosphate, magnesium and potassium are frequently low and require repeated supplementation
- Enteral feedings should be initiated early- 60 g of protein daily is reasonable in most patients
- If enteral feeds are contraindicated, parenteral nutrition should be considered- both these decrease risk of GI bleeding due to stress ulcers

# Prognostic models in Acute Liver Failure

Etiologies with good transplant free survival ( $\geq 50\%$ )

- Acetaminophen
- Hepatitis A
- Shock liver
- Pregnancy related liver disease

Currently available prognostic scoring systems do not adequately predict outcome and determine candidacy for liver transplantation. Reliance entirely upon these guidelines is thus not recommended.



# Questions & Discussion