Acute Liver Failure

Catherine Frenette, MD, FAST, AGAF
Medical Director of Liver Transplantation
Scripps Center for Organ Transplantation
Director, Liver and Hepatocellular Cancer Program
Scripps MD Anderson Cancer Center
La Jolla, CA

Acute Liver Failure

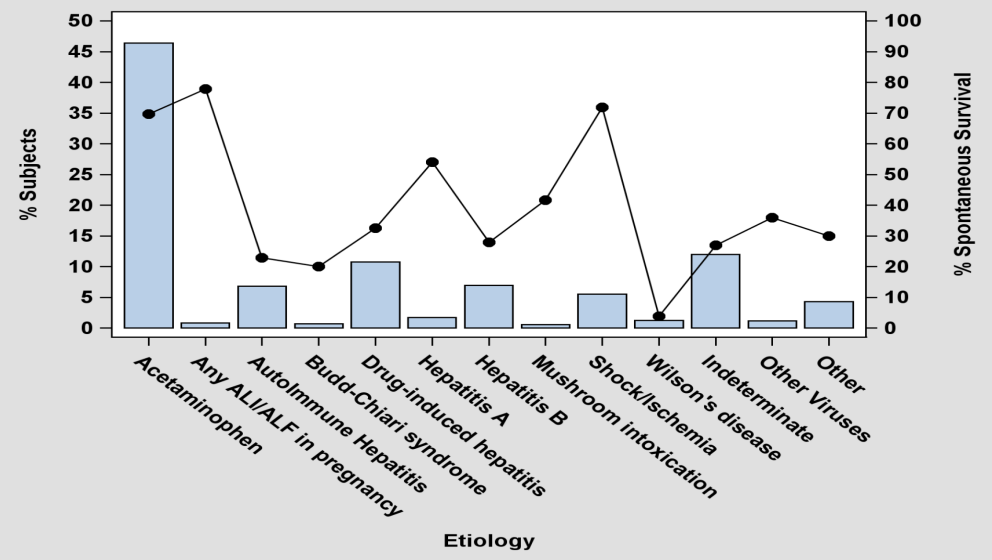
- Rapidly progressive (<8 wks/UNOS), often fatal syndrome characterized by
  - Altered mentation/encephalopathy
  - Coagulopathy (INR >2.0)
  - Jaundice
- Time frame <24-26 weeks
  - Hyperacute: <7 days from presentation to encephalopathy
  - Acute: 7-21 days to encephalopathy
  - Subacute: 21 days-26 weeks to encephalopathy, often developing renal failure and portal hypertension
- No prior history of chronic liver disease or cirrhosis
  - Wilson's disease can be considered ALF for listing purposes even with known history or cirrhosis
  - Autoimmune hepatitis or vertically acquired HBV often presents with ALF
    - Not previously recognized
    - Recognized but medications stopped

ALF: Summary of a Workshop

- Relatively rare disease: 2000 cases/year
- Accounts for ~4-5% of all transplant listings
- Etiology not identified 15% adults/50% peds
- Course variable with high mortality
- 45% spontaneously recover
- 25% transplanted
- 30% death (sepsis and cerebral edema)

Lee WM et al, Hepatol 2008

Etiology of ALF in Adults



Bari et al, Prac Gastro & Hep 2016

Baseline Characteristics

Feature	Acetaminophen (n = 532)	Drugs (n = 133)	Indeterminate (n = 161)	Hepatitis A (n = 31)	Hepatitis B (n = 83)	All Others (n = 207)
Age (years)*	37 (28–45)	46 (33–56)	38 (26–50)	47 (40–57)	42 (29–54)	42 (29–56)
Female Sex	76%	67%	58%	45%	42%	76%
Jaundice to Coma (days)*	0 (0–1)	9 (3–20)	9 (2–20)	3 (1–8)	7 (2–14)	7 (1–17)
Coma grade ≥ 3	52%	38%	50%	55%	54%	41%
ALT (U/L)*	4067 (2138–6731)	600 (260–1537)	847 (396–2111)	2404 (1367–3333)	1707 (745–2815)	650 (172–1867)
Bilirubin (mg/dL)*	4.5 (2.9–6.6)	20.2 (12.1–28.3)	23.0 (9.2–29.7)	11.9 (9.7–27.5)	19.7 (12.4–25.6)	15.3 (6.3–26.7)
Spontaneous Survival	65%	29%	25%	58%	25%	34%
Transplantation	9%	41%	43%	29%	47%	33%
Death Without Transplantation	26%	31%	32%	13%	28%	33%

Summarized and updated (after the workshop) from the ALF Study Group database, 1998-2007.[3,4]
* Median values (Q_1-Q_3).

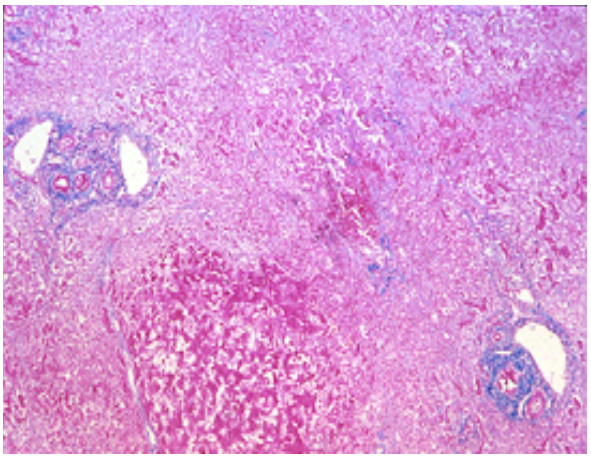
Lee WM et al, Hepatol 2008

Clinical Pearls

- HEV: travel to Eastern Europe, Asia, India, Mexico. More severe in pregnancy
- HSV: neonates or pregnancy, steroid use, HIV, cancer, myelodysplastic syndromes. URI and hepatitis, no rash in 50%. Treat early with acyclovir
- VZV: immunosuppressed, hepatitis may predate rash or occasionally no rash
- Aminita phalloides: severe GI symptoms (N/V/D) within hours to a day from ingestion, liver injury 2 days later
- Wilsons: very low alk phos or uric acid, Bili:alk phos >2, Coombs negative hemolytic anemia with bili >20 ng/mL

Role of Liver Biopsy

- Always do transjugular route
- Unreliable in predicting clinical outcomes
- Not recommended in most cases
- Consider when autoimmune hepatitis, metastatic cancer (breast, small cell lung, melanoma), myeloma, lymphoma, or HSV suspected



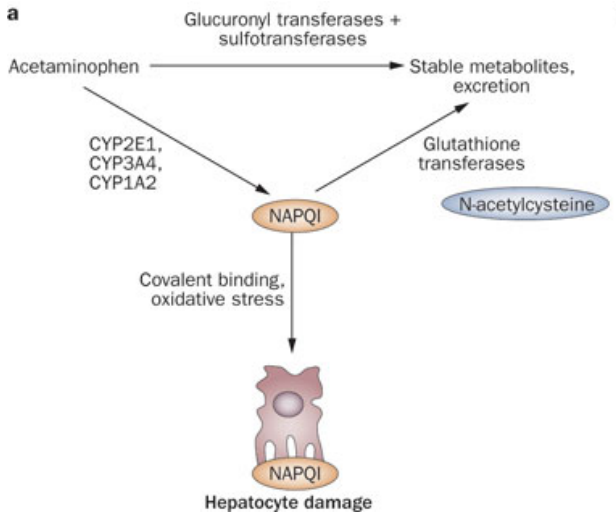
Lee et al, Hep 2011; Flamm et al, Gastro 2017

Therapies

Etiology	Potential therapies
TOXIC	
Acetaminophen	N-acetyl cysteine
Amanita poisoning	Charcoal, penicillin, silibinin
VIRAL	
Herpes simplex virus	Acyclovir
Acute heptatitis B	Nucleos(t)ide
METABOLIC	
Wilson's disease	Copper chelation, plasmapheresis, antioxidant
Autoimmune hepatitis	Corticosteroids
VASCULAR	
Acute Budd Chiari	Directed thrombolysis, TIPS
PREGNANCY	
Acute fatty liver of pregnancy/HELLP	Urgent delivery

Acetaminophen

- Still a large problem in US (especially combination narcotic/APAP)
- ~50/50 suicidal vs unintentional
- Relatively low mortality compared to other ALF cases
- 19% of indeterminant cases had APAP adduct level at 7 days



Lee, et al, Hep 2008;
Tujios and Fontana Nature Rev Gastro Hep 2011

Acetaminophen

Table 2. Comparison of Intentional and Unintentional Acetaminophen Overdose

Feature	Intentional (n = 122)	Unintentional (n = 131)	*P* Value
Age (years)*	34 (17–68)	38 (18–76)	NS
Female Sex	74%	73%	NS
Total Dose (grams)*	25 (1.2–90)	20 (2.5–180)	NS
Dose per day (grams)*	25 (1.2–90)	7.5 (1.0–7.8)	NS
Coma Score ≥ 3	39%	55%	
Maximum ALT (U/L)*	5326 (179–19,826)	3319 (176–18,079)	NS
History of depression	45%	24%	
Antidepressant use	38%	37%	NS
Narcotic compound	18%	63%	
Multiple preparations	5%	38%	
Spontaneous survival	66%	64%	NS
Transplantation	7%	9%	NS
Death without transplantation	27%	27%	NS

Summarized from reference 50 on a prospective consecutive series of 275 cases of ALF due to acetaminophen overdose, in 22 of whom the intent could not be determined.
* Median values (range).

Lee WM et al, Hepatol 2008

Treatment of APAP Hepatotoxicity

- Activated charcoal if within a few hours
  - Best of <1 hour, reasonable up to 3-4 hours
  - 1 gm/kg oral slurry
- Initiate NAC (preferably IV)
  - No prospective studies to support benefit if >24 hours
  - Often given up to 72 hrs after ingestion
  - 150 mg/kg IV load followed by gtt
  - Controversial stop at 72 hrs vs liver recover
  - Side effects: allergic reaction, bronchospasm, asthma

NAC for Non-APAP ALF?

- Prospective trial of 173 patients with primary endpoint of overall survival at 3 weeks
  - 70% NAC vs 66% placebo (not significant)
- Transplant free survival 40% vs 72%
  - Confined to encephalopathy grade 1-2
    - 52% NAC vs 30% placebo
  - Worse in encephalopathy grade 3-4
    - 9% NAC vs 22% placebo
- Transplant rate lower 32% NAC vs 45% placebo (not significant)

Lee WM et al, Gastro 2009

NAC for Non-APAP ALF?

- NAC may improve spontaneous survival
  - When given during early encephalopathy grade 1-2
  - DILI and HBV may benefit
  - Large amount of idiopathic cases are unknown APAP
- Guidelines:
  - AASLD: use in cases where it is possible APAP could be involved, for DILI may be beneficial
  - EASL: use in early stage in all ALF
  - AGA: use in non-APAP ALF only in context of clinical trials

Lee et al, Hepatol 2011
EASL Guidelines 2017
Flamm et al, Gastro 2017

Drug Induced Liver Injury

- Most drug induced liver injuries occur within first 6 months of administration
- Generally patients present in a subacute fashion
  - Lower AST/ALT, higher bilirubin
  - Portal hypertension and shrunken nodular liver mimicking cirrhosis
  - Unfavorable transplant-free survival
  - 94% post transplant survival
- Corticosteroids are only indicated if there is also a hypersensitivity reaction (DRESS) or autoimmune reaction

Lee et al, Hepatol 2011

DRESS = drug rash, eosinophilia, systemic symptoms

Drug Induced Liver Injury

Table 3. Some Drugs Which May Cause Idiosyncratic Liver Injury Leading to ALF

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

Lee et al, Hepatol 2011

Wilson Disease

- Nearly uniformly fatal without transplant
- UNOS exception 1A can be assigned even with known prior liver disease or cirrhosis present
- Clues to diagnosis
  - Coombs negative hemolytic anemia and bilirubin >20 mg/dL
  - Very low alkaline phosphatase and/or uric acid
  - Bili:alk phos ratio >2
  - Ceruloplasmin can be normal in up to 15% (and low in 50% of ALF from other causes)
  - Kayser-Fleischer rings present in 50%
- Treatment
  - Can attempt to acutely lower copper to prevent further hemolysis with albumin dialysis, plasmapheresis, plasma exchange
  - Do not attempt chelating agents
  - Transplant

Lee et al, Hepatol 2011

Autoimmune Hepatitis

- May account for up to 30% of indeterminant cases
  - 25-39% ANA negative or weakly positive and normal IgG
  - Liver biopsy can be helpful
- Consider corticosteroids for some with early stage ALF without multi-organ failure
  - Prednisone or prednisolone 40-60 mg/d
  - Methylprednisolone 60 mg IV/d
  - Do not treat indefinitely
- Septic complications from steroids can jeopardize transplant
  - if multilobular necrosis and failure to improve within 2 weeks, stop steroids
  - Jaundice and failure to improve MELD by 2 points in 7 days, stop steroids

Czaja et al, Alim Pharm Ther 2013

Aminita Phalloides Poisoning

- "Death Cap" mushroom, found mainly summer and autumn
- Ingestion of 30g (1 oz) or ½ cap likely lethal without transplant
- Severe GI symptoms within hours to 1 day of ingestion, then presents 1-2 days later with liver failure
- Amatoxin taken up by hepatocyte, inhibits RNA polymerase II, excreted in bile, and reabsorbed causing more damage
- Liver primarily affected, can also cause renal failure
- Treatment:
  - gastric lavage with activated charcoal
  - Nasobiliary drainage
  - Penicillin G 1 gm/kg/d IV plus NAC
  - Silibinin IV 30-40 mg/kg/d x 3-4 days (investigational in US)

Czaja et al, Alim Pharm Ther 2013

Transplant Listing

- UNOS Criteria for Status 1A listing
  - Life expectancy without a liver transplant of less than 7 days and has at least one of the following conditions:
    - Fulminant liver failure, defined as the onset of hepatic encephalopathy within 56 days of the first signs or symptoms of liver disease. In addition, the candidate
      - Must not have a pre-existing diagnosis of liver disease
      - Must currently be admitted to the intensive care unit
      - Must meet at least one of the following conditions:
        - Is ventilator dependent
        - Requires dialysis, continuous veno-venous hemofiltration (CVVH), or continuous veno-venous hemodialysis (CVVHD)
        - Has an INR greater than 2.0
    - Anhepatic
    - Primary nonfunction of a transplanted whole liver or liver segment (with certain lab parameters)
    - Hepatic artery thrombosis within 7 days of transplant (with certain lab parameters)
    - Acute decompensated Wilson's disease

UNOS/OPTN Policy 9.1.A, effective 6/8/2020, page 163-164

King's College Criteria

KING'S COLLEGE HOSPITAL CRITERIA FOR LIVER TRANSPLANTATION

ACETOMINOPHEN-INDUCED ACUTE LIVER FAILURE

Current criteria*	Modified criteria ◊
List for transplantation if:	**Strongly consider listing for transplantation if:**
Arterial pH <7.3 after adequate fluid resuscitation	Arterial blood lactate concentration >3.5 mmol/l after early fluid resuscitation
List for transplantation if all three of the following occur within a 24-h period:	**List for transplantation if:**
• Creatinine >300 µmol/l (>3.4 mg/dl)	Arterial pH <7.3, or arterial blood lactate concentration >3.0 mmol/l after adequate fluid resuscitation
• PT >100 s (INR >6.5)	
• Grade III/IV encephalopathy	**List for transplantation if all three of the following occur within a 24-h period:**
	• Creatinine >300 µmol/l (>3.4 mg/dl)
	• PT >100 s (INR >6.5)
	• Grade III/IV encephalopathy

*O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97:439–445.
◊Bernal W, Donaldson N, Wyncoll D, Wendon J. Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. Lancet 2002;359:558–563.

NON-ACETOMINOPHEN-INDUCED ACUTE LIVER FAILURE

List for transplantation (regardless of grade of encephalopathy) if:
• PT >100 s (INR >6.5)
List for transplantation (regardless of grade of encephalopathy) if any three of the following present:
• Cryptogenic, halothane, or other drug toxicity etiology
• Age < 10 yr or > 40 yr
• Jaundice to encephalopathy interval > 7 days
• PT > 50 s (INR > 3.5)
• Serum bilirubin > 18 mg/dl

Other Criteria for Prognosis

- AGA guidelines recommend using MELD score over King's College Criteria for prognostic scoring system
  - MELD score > 30.5 predicts need for OLT
    - Pooled sensitivity 77%, pooled specificity 72%
  - AASLD guidelines recommend King's College Criteria over MELD
    - Sensitivity 68-69%, specificity 82-92%
  - EASL notes even low grade encephalopathy may indicate extremely poor prognosis in subacute presentations, and prognosis worse in patients with more severe liver injury, extrahepatic organ failure, and subacute presentations

Lee et al, Hep 2011; Flamm et al, Gastro 2017; EASL JHep 2017

Management of the Patient with ALF

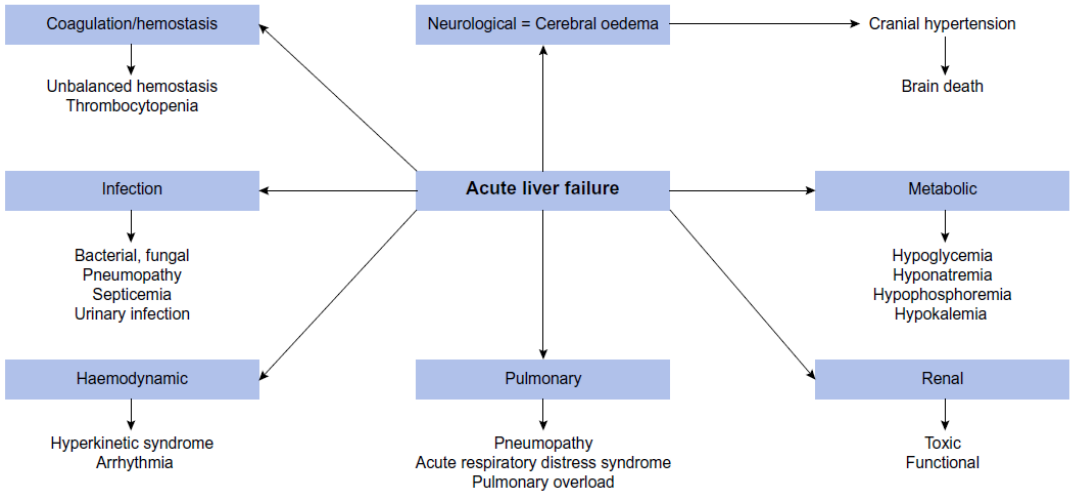


Fig. 2. Main organ specific complications in ALF.

EASL JHep 2017

Management of the Patient with ALF

- Foley, arterial line, central venous lines
- Avoid lactated ringers
  - Albumin preferred, especially if serum albumin <3 mg/dL
- Enteral nutrition when able
- PPI recommended for stress ulcer prophylaxis
- Norepinephrine is first pressor of choice (more predictable cerebral perfusion)
  - Vasopressin causes some cerebral vasodilation
  - Epinephrine decreases mesenteric blood flow, compromising hepatic function

Nanchal, Crit Car Med 2020

Cerebral Edema in ALF

- Development of CE/ICH defines prognosis
  - 30% of patients with CE will herniate while awaiting an organ
- Possible long term neuro effects in survivors
  - 25-35% in grade 3 HE, 65-75% in grade 4 HE
- Related to cytokine release and inflammatory mediators, causing vasodilation and cerebral hyperemia, along with increased ammonia causing glutamine/alanine increase in astrocytes

O'Grady JG, et al. *Gastro*, 1989.
Jalan R. *Sem in Liver Dis.* 2003
Lee, Larson, Stravitz, Hep, 2011.

Cerebral Edema in ALF

- Clinical signs not reliable, ICP can silently increase until late stages
- Arterial ammonia levels >100 mmol/L herald impending herniation and poor outcomes
- Transcranial dopplers can be useful, CT somewhat insensitive, and occasionally ICP monitor required
- Grade 3-4 encephalopathy patients should be intubated to prevent aspiration
- Continuous renal replacement therapy recommended even in setting of normal renal function for removal of fluid and ammonia

O'Grady JG, et al. *Gastro*, 1989.
Jalan R. *Sem in Liver Dis.* 2003
Lee, Larson, Stravitz, Hep, 2011.

Cerebral Edema in ALF

Table 2. Interventions for intracranial hypertension

Intervention	Appropriate in Most Cases?	Target	Notes/Caveats
Head-of-bed elevation	Yes	>30 degrees	
Vasopressors	Yes	MAP > 75 mm Hg and cerebral perfusion pressure 60–80 mm Hg	If patient not spontaneously meeting targets
Hyperosmolar therapy	Yes	Serum sodium 145–155 mEq/L	In highest-risk patients (severe encephalopathy)
Intravenous mannitol	Yes	Serum osmolality 300–320 mmol/kg	Patient must have intact renal function
Hyperventilation	No	Pa_{CO_2} < 34	Acutely reduces ICP but ineffective for prolonged periods; may ultimately impair cerebral perfusion
Therapeutic hypothermia	No	32°–34°C	Some promise in animal studies and small trials; recent randomized trials do not support widespread use (10)

Definition of abbreviations: ICP = intracranial pressure; MAP = mean arterial pressure.

- Lactulose used but with little data; little data on Rifaximin
- Small doses of propofol preferred sedation

EASL Guidelines 2017
Flamm et al, Gastro 2017
Poston et al, Ann Am Thorac Soc 2017

Infection

- Bacterial +/- fungal sepsis frequent cause of death
  - Often in absence of fever or leukocytosis
- Surveillance cultures recommended in all
- Empiric antibiotics not recommended until patient develops grade 3-4 encephalopathy, clinical signs of infection, or elements of SIRS
  - Based on local resistance profiles
- Consider antifungal therapy in patients with prolonged critical care support

EASL JHep 2017

Coagulopathy

- Do not correct coagulopathy prophylactically
  - Increases volume overload
  - Confuses/obscures clinical picture (INR for prognosis)
  - Does not reduce transfusion requirements
- Administer vitamin K 5-10 mEq SQ or IV x3 days
- Use thromboelastogram (TEG) for coagulation testing prior to procedures rather than INR, fibrinogen, PTT, or platelets

ALF Checklist

DO NOT PLACE IN THE MEDICAL RECORD

ADMISSION AND DIAGNOSIS ALF CHECKLIST

THE FOLLOWING ARE TO BE DONE ON ADMISSION AND DAILY IN ALL CASES OF ALF:

- ❑ Neuro checks every 1-2 hours
- ❑ Head of the bed at 30°
- ❑ Head in neutral position
- ❑ Minimize stimulation (tracheal suctioning, chest physiotherapy, sternal rubbing)
- ❑ N-acetylcysteine (NAC) IV until INR <1.5 or resolution of encephalopathy*
- ❑ CXR and surveillance cultures (blood, urine, sputum) on admission and every 24-48 hrs
- ❑ Monitor blood glucose every 1-2 hours
- ❑ Avoid nephrotoxic drugs (aminoglycosides, NSAIDs, neomycin, etc) and IV contrast
- ❑ DVT prophylaxis (sequential compression device) despite coagulopathy; avoid heparin
- ❑ PPI for stress ulcer prophylaxis
- ❑ Communication: 1) intensivist and/or transplant hepatologist, 2) nurse, 3) patient's family

POSSIBLE ETIOLOGY	DIAGNOSTIC ITEMS TO DO IN *ALL CASES OF ALF*	DIAGNOSTIC ITEMS TO *CONSIDER*	SPECIFIC THERAPIES
Drug/toxin	❑ Obtain 6-month medication/toxin/ingestion history including OTC supplements, herbals, wild mushrooms, weight loss drugs ❑ Urine and serum toxicology screens ❑ Acetaminophen level		Acetaminophen toxicity: NAC Mushroom poisoning: Charcoal, NAC, penicillin G and/or silibinin**
Viral	❑ Anti-HAV IgM ❑ HBsAg, anti-HBc IgM, HBV DNA (quantitative) ❑ Anti-HCV, HCV RNA	· Anti-HEV · HSV DNA · EBV DNA · CMV DNA · Anti-HDV/HDV RNA	HBV: Entecavir HSV: Acyclovir
Autoimmune	❑ Antinuclear antibody ❑ Anti-smooth muscle antibody/anti-actin antibody ❑ Immunoglobulin G	· Anti-liver/kidney microsomal antibody · Liver biopsy	Corticosteroids
Vascular Budd Chiari Ischemia	❑ Abdominal ultrasound with Doppler	· CT/MRI · Assess for hypercoagulable state including search for malignancy · Interventional radiology consultation · Echocardiography/ECG	Budd Chiari: Anticoagulation, TIPS
Wilson	❑ Check for hemolytic anemia (high indirect bilirubin), low alkaline phosphatase, renal failure, acidosis	· Ceruloplasmin · 24-hour urine for copper · Serum copper · Ophthalmology consultation to look for Kayser-Fleischer rings	Consider early CRRT
AFLP / HELLP		· β-HCG · Obstetrics consultation	Early delivery
Malignancy		· CT/MRI · Liver biopsy	
Indeterminate		· Liver biopsy	

OTC, over-the-counter; NAC, N-acetylcysteine; CRRT, continuous renal replacement therapy
*For all patients with ALF and encephalopathy grade I/II regardless of etiology, and for all cases of suspected acetaminophen toxicity
**Not FDA approved

Instructional video:
http://alfchecklist.com/video

DO NOT PLACE IN THE MEDICAL RECORD

ADMISSION AND DAILY ALF CHECKLIST

THE FOLLOWING ARE TO BE EVALUATED AT THE TIME OF ADMISSION AND DAILY:

1. NEUROLOGIC

Abrupt deterioration in mental status?
- ❑ Yes→ Head CT to look for intracranial hemorrhage

Serum sodium <145 mMol/L?
- ❑ Yes→ Consider using hypertonic saline for prophylaxis of intracranial hypertension to maintain serum Na between 145-150 mMol/L; carefully monitor rate of Na rise; discuss serum Na goal with healthcare team if patient on CRRT

Intubated, agitated or in pain?
- ❑ No → Avoid sedating medications (benzodiazepines, narcotics, central-acting anti-emetics)
- ❑ Yes→ Use propofol and/or fentanyl

Spontaneous hypothermia (34-37 °C)?
- ❑ Yes→ Do not warm patient

Encephalopathy grade III/IV?
- ❑ Yes→ Consider mannitol 0.25-0.5 g/kg IV q6 hours if serum osmolality <320 mOsm/L or hypertonic saline boluses for treatment of suspected intracranial hypertension
- ❑ Yes→ Consider intracranial pressure monitoring
  - Goal intracranial pressure <25 mm Hg
  - Goal cerebral perfusion pressure 50-80 mm Hg

2. PULMONARY

Encephalopathy grade III/IV?
- ❑ Yes→ Intubate; prefer low tidal volume ventilation to avoid acute lung injury

Intubated and spontaneously hyperventilating?
- ❑ Yes→ Do not correct ventilation

3. INFECTIOUS DISEASE

1) Progression of encephalopathy or grade III/IV or 2) SIRS or 3) clinical deterioration or 4) patient listed for transplant?
- ❑ Yes→ Consider broad-spectrum antibiotics

4. CARDIOVASCULAR

Mean arterial pressure (MAP) <75 despite volume repletion AND encephalopathy grade III/IV?
- ❑ Yes→ Begin vasopressors (prefer norepinephrine over epinephrine or vasopressin)
- ❑ Yes→ Consider trial of hydrocortisone

5. RENAL

1) Oliguria or 2) rise in creatinine >0.3 mg/dL or 3) ammonia >150 μM or 4) volume overload or 5) established/suspected intracranial hypertension?
- ❑ No → Consider renal consultation/early hemodialysis line placement
- ❑ Yes→ Initiate CRRT (CRRT preferred over intermittent HD even if hemodynamically stable)

6. HEMATOLOGY

Clinically significant bleeding?
- ❑ No → Do not correct INR
- ❑ Yes→ Correct thrombocytopenia, hypofibrinogenemia and coagulopathy

Planned invasive procedure?
- ❑ No → Do not correct INR
- ❑ Yes→ Correct thrombocytopenia and hypofibrinogenemia (INR does not predict bleeding risk in patients with ALF)

7. ENDOCRINE

Glucose <80 mg/dL?
- ❑ Yes→ Dextrose

Glucose >180 mg/dL?
- ❑ Yes→ Insulin

8. GASTROINTESTINAL

Enteral feeding possible (PO or NG)?
- ❑ Yes→ Begin as early as possible

9. EARLY TRANSPLANT EVALUATION

Encephalopathy?
- ❑ Yes→ Consult transplant center/transplant hepatologist early

Potential liver transplant candidate?
- ❑ Yes→ Begin transplant evaluation per center protocol

All criteria for Status IA listing met?

All 3 of following criteria must be met:
1. Onset of encephalopathy within 8 weeks of first symptoms of liver disease
2. In the ICU
3. a) INR >2 or b) intubated or b) on CRRT
- ❑ Yes→ Consider listing, in consultation with transplant team

NAC, N-acetylcysteine; CRRT, continuous renal replacement therapy

Instructional video:
http://alfchecklist.com/video

Fig 3. Final checklist.

A checklist may be useful especially in training institutions

http://alfchecklist.com

Fix et al, PLOS One 2016

Conclusions

- Acute liver failure is a rare emergency
- Understanding the time to onset, etiology, and prognosis can help dramatically with knowing best steps in care
- Multiple organ systems are involved and each one needs special understanding for care of these patients
- Most care is best done in a transplant center where liver transplant can be offered in those cases with poor transplant free survival

MOC QUESTION

AASLD

A 32 year old man with Wilson's Disease comes in to the hospital with confusion. He has had known Wilson's disease for approximately 12 years, and was on therapy with Trientene. He recently had some difficulties with getting refills from the prescriber's office, and has been out of his medications for two weeks. On presentation, he is confused but responsive. He has asterixis. His vital signs are stable.

MOC QUESTION

AASLD

Laboratory Test	Result	Reference Range
Albumin, serum	3.1 g/dL	3.5-5.5 g/dL
Aminotransferase, serum aspartate (AST, SGOT)	850 U/L	10-40 U/L
Aminotransferase, serum alanine (ALT, SGPT)	300 U/L	10-40 U/L
Alkaline phosphatase, serum	55 U/L	30-120 U/L
Bilirubin, serum (total)	14.1 mg/dL	0.3-1.0 mg/dL
Creatinine	3.4 mg/dL	15–25 mg/kg body weight/24 hr
Sodium, serum	135 mEq/L	136-145 mEq/L
Hemoglobin, blood	7.5 g/dL	14-18 g/dL (male)
INR	2.3	1.0

MOC QUESTION

AASLD

QUESTION/ POLL

What is the best next step in treatment?

A. List for liver transplant, Status 1A
B. List for liver transplant, MELD 37
C. Restart trientene
D. Urgent plasma exchange

MOC QUESTION

AASLD

ANSWER RATIONALE

A. List for liver transplant, status 1A

- Acute liver failure Wilsons disease can occur as a new presentation or after stopping therapy. Prognosis is poor without liver transplant, and Wilsons disease is one of the few cases where patients are listed as a status 1A even in the setting of know chronic liver disease rather than MELD score listing
- Restarting trientene is unlikely to result in significant recovery
- Plasma exchange is sometimes used to acutely lower serum copper and limit further hemolysis and liver damage, but is unlikely to result in recovery.

MOC QUESTION

AASLD

REFERENCES

- Lee WM, Larson AM, Stravitz RT. AASLD position paper: the management of acute liver failure: update 2011. Hepatology 2012 Mar;55(3):965-967, PMID 22213561
- UNOS/OPTN Policy 9.1.A, effective 6/8/2020, page 163-164.

MOC QUESTION

AASLD

A 32 year old woman comes in with upper respiratory symptoms and fever. She is 28 weeks pregnant, and so far has had an uncomplicated pregnancy. She denied any sick contacts. She has well controlled systemic lupus erythematosus and is on hydroxychloroquine 200 mg daily and prednisone 5 mg daily. She denies any other medications or herbal supplements. She does not drink, smoke, or use illicit drugs. She reports family history of diabetes. Physical exam is notably for right upper quadrant abdominal tenderness, gravid uterus. Lung exam is normal. She has a fever to 39.2, and is lethargic.

MOC QUESTION

Laboratory Test	Result	Reference Range
Albumin, serum	3.2 g/dL	3.5-5.5 g/dL
Aminotransferase, serum aspartate (AST, SGOT)	2607 U/L	10-40 U/L
Aminotransferase, serum alanine (ALT, SGPT)	2364 U/L	10-40 U/L
Alkaline phosphatase, serum	130 U/L	30-120 U/L
Bilirubin, serum (total)	3.1 mg/dL	0.3-1.0 mg/dL
Creatinine	3.4 mg/dL	15–25 mg/kg body weight/24 hr
Sodium, serum	135 mEq/L	136-145 mEq/L
Hemoglobin, blood	11.5 g/dL	12-16 g/dL (female)
INR	1.4	1.0

Ultrasound duplex of liver is normal. Ultrasound of uterus is normal with viable fetus.
Hepatitis A, B, and C is all negative (IgM and IgG)

MOC QUESTION

QUESTION/ POLL

Which of the following is the best step in treatment?

A. Urgent liver transplant
B. Urgent delivery of fetus
C. IV steroids
D. IV acyclovir
E. Anticoagulation

ANSWER RATIONALE

D. IV Acyclovir

- Herpes hepatitis requires a high index of suspicion and has a high mortality with progression to liver failure, with mortality rates approaching 90%. It most commonly affects women in the second and third trimester of pregnancy, and in up to 50% of cases is not associated with the characteristic skin rash. Therapy with IV acyclovir is life-saving, and must be instituted quickly. Patients present with a characteristic anicteric hepatitis with very high liver enzymes in the setting of relatively low or normal bilirubin, and often have fevers and concomitant upper respiratory symptoms. It is best diagnosed with HSV PCR or liver biopsy.
- Urgent liver transplant is not the best treatment as she may have a response to IV acyclovir and preclude the need for liver transplant. In addition, she does not yet meet the criteria for acute liver failure Status 1A transplant since her INR is less than 2.
- Delivery of fetus is not recommended as this does not change the outcomes of the acute herpes hepatitis and this liver injury is not pregnancy related.
- IV steroids would be appropriate for acute autoimmune hepatitis, which this patient is at risk for given her underlying lupus, but is not commonly associated with fevers and upper respiratory symptoms. She may require stress dose steroids because of her chronic prednisone use, but this is not the best answer.
- Anticoagulation may be required if she had acute thrombosis of hepatic veins or portal veins, which she is at risk for with pregnancy, but her ultrasound was normal so this diagnosis is very unlikely.

REFERENCES

- Norvell JP, Blei AT, Jovanovic BD, Levitsky J. Herpes simplex virus hepatitis: an analysis of the published literature and institutional cases. Liver Transpl 2007 Oct;13(10):1428-24. PMID 17902129