Acute Liver Failure in ICU

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I have no disclosures relevant to this presentation.

OUTLINE

- Definition
- Epidemiology
- Pathogenesis
- Specific Therapies
- Management of Complications
- Assessment of Prognosis
- Outcomes

Acute Liver Failure

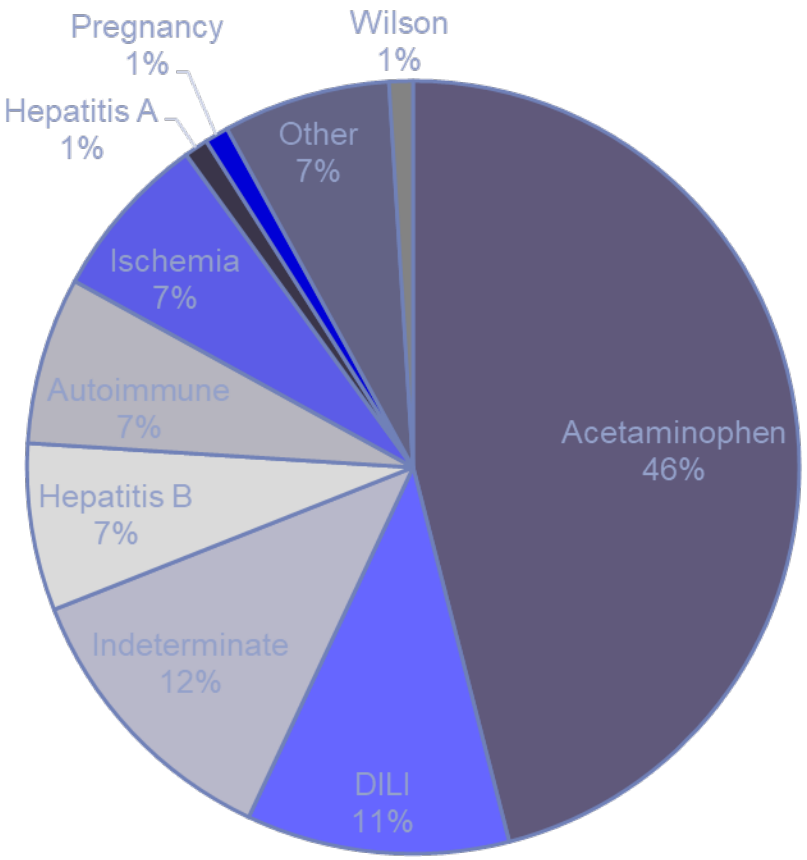
Most reliable defining markers:

- INR ≥ 1.5
- Altered mentation or encephalopathy
- Length of illness < 26 weeks
- No preexisting liver disease

Background on ALF

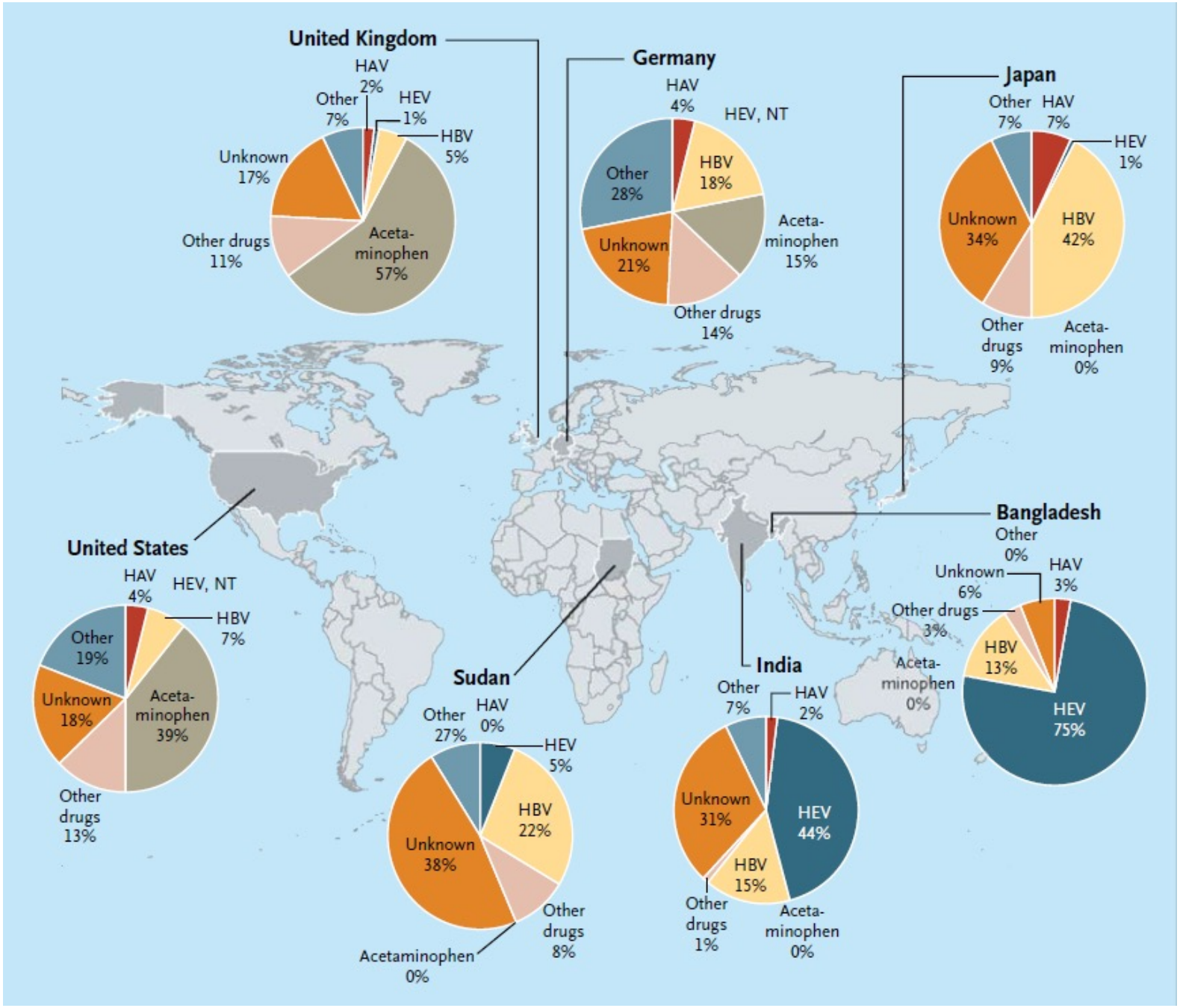
- Rare: ~2,000 cases/year in U.S.
- All patients should be cared for in ICU
- No one medical center can study the condition
- Variety of etiologies
- No viable treatment for all patients
- Morbidity/mortality 94% prior to transplant
- Patients can be listed UNOS Status 1 for 7 days
- Prior to 1980's, HBV was >40% cases

Etiology of ALF in Adults in the United States



N=2614, 1/1998-3/2019.

Lancet 2019; 394: 869-881.



NEJM 2013; 369: 2528.

Etiology and Clinical Characteristics of ALF

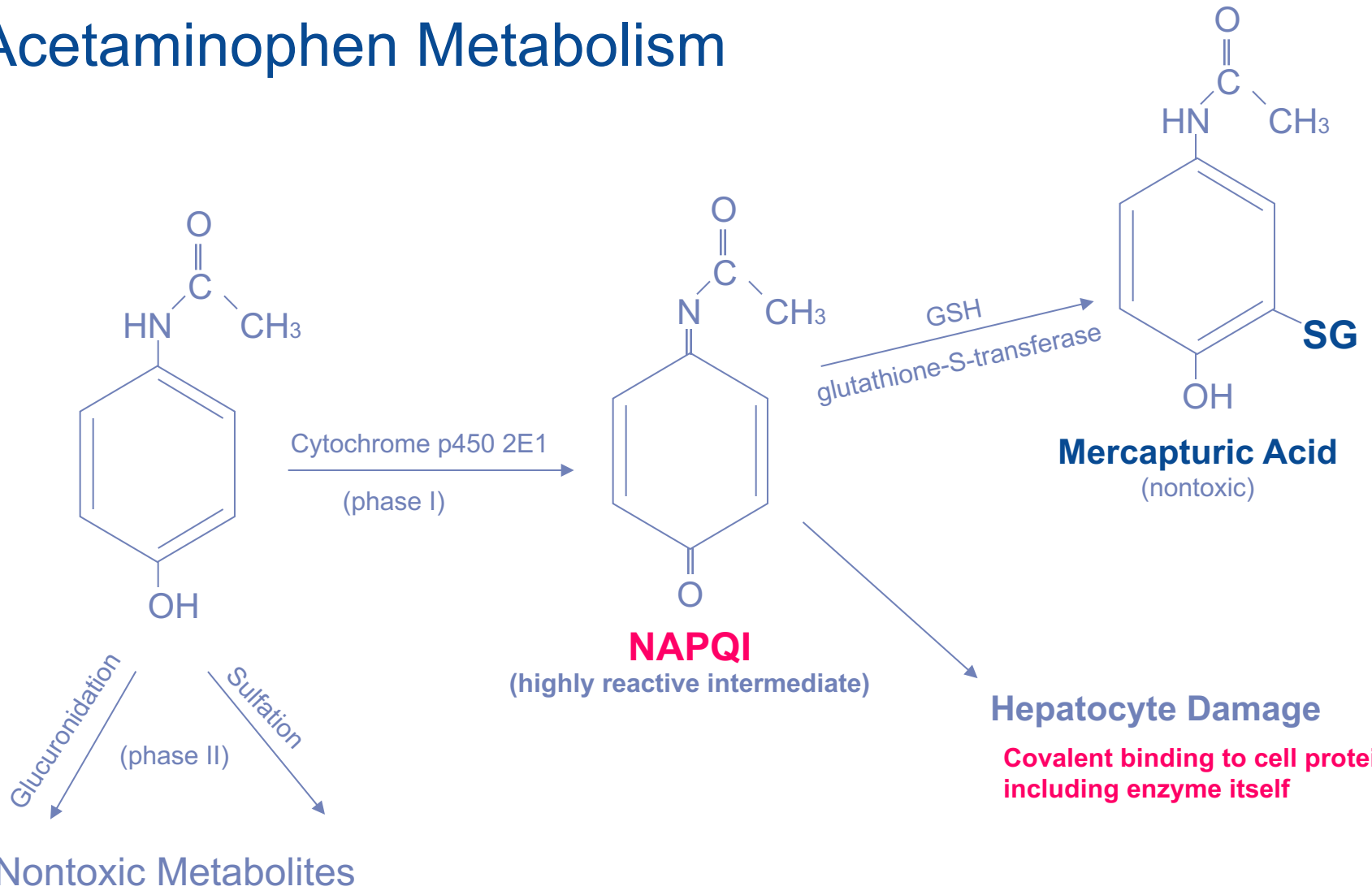
	Acetaminophen	Drugs	Ischemia	Hep A	Hep B	All Others
Median Age	37	47	53	50	45	40
Female Sex	75%	67%	58%	44%	45%	64%
Jaundice to Coma (Days)	1	12	2	4	8	7
Coma ≥ 3	54%	36%	56%	54%	51%	44%
Median ALT	3780	654	2311	2229	1410	758
Median Bilirubin	4.3	19.6	3.8	12.0	19.2	17.2
Transplant Free Survival	65%	24%	57%	51%	19%	22%
Transplant	9%	39%	2%	33%	40%	36%
Overall Survival	72%	58%	58%	77%	53%	55%

Lancet 2019; 394: 869-81.

Acetaminophen: Scope of Problem

- Billion dollar problem: OTC, > 300 brands
- Unique dose-related toxicity
- 100,000 calls to Poison Control annually
- 50,000 ER visits/year
- 10,000 hospitalizations/year
- ~100-500 deaths/year
- Hydrocodone/APAP is number 1 generic prescription drug – >100 million prescriptions/year (Lorcet, Lortab, Maxidone, Vicodin, Zydone)
- Since 1998 U.K. has limited package size to 16-24 and employed blister packs → decreased complications by 27-33% (hospital admissions, transplants, deaths)
- Since 2009, FDA limits amount of prescription acetaminophen paired with narcotics to 325mg

Acetaminophen Metabolism



Comparison of Intentional and Unintentional Acetaminophen Overdose

	Intentional	Unintentional
Age (years)	34	38
Female Sex	74%	73%
Total Dose (g)	25	20
Coma ≥ 3	39%	55%
Maximum ALT	5326	3319
History of Depression	45%	24%
Antidepressant Use	38%	37%
Narcotic Compound	18%	63%
Multiple Preparations	5%	38%
Transplant Free Survival	66%	64%
Transplantation	7%	9%
Death Without Transplant	27%	27%

Hepatology 2008; 47: 1401-1415

Drug Induced Liver Injury

- 11% ALF cases overall
- 67% Women
- Outcome poor: ~24% survive without transplant
- Most cases occur within first 6 months after drug initiation

Antimicrobials: 46%

Complementary alternative medications or supplements: 23%

Antimetabolites/NSAIDS/biologic agents: 27%

Drug Induced Liver Injury

http://livertox.nlm.nih.gov – DILIN network

Isoniazid
Sulfasalazine
Phenytoin
Statins
Propylthiouracil
Ciprofloxacin
Nitrofurantoin
Cocaine
Valproic Acid
Amiodarone
Dapsone
Didanosine
Efavirenz
Carbamazepine
MDMA (Ecstasy)
Labetalol

Itraconazole
Nicotinic Acid
Ketoconazole
Doxycycline
Diclofenac
Trimethoprim-Sulfa
Rifampin-Isoniazid
Amoxicillin-Clavulanate
Kava Kava
Herbalife
Hydroxycut
Comfrey
Senecio
Greater celandine
He Shon Wu
LipoKinetix
Ma Huang

Viral Hepatitis causing ALF

- HBV = 7%, HAV=1%, HCV = 0
- Hep A in US: epidemics related to food contamination
- Hep B most common viral etiology of ALF in US: chemotherapy reactivation
- Hepatitis E (endemic in Russia, Pakistan, India, Mexico), but cases in US without travel are more common
- Parvovirus B19, HDV, SEN virus, Dengue, HSV, VZV
- No reported, definitive cases of COVID-19 causing ALF

Wilson Disease

- 5% present with ALF
- Nearly always fatal without transplant
- Clinical characteristics:
  - High bilirubin > 30mg/dl
  - Low Alkaline Phosphatase <20
  - ALP: Bilirubin ratio <2
  - Hemolytic anemia
  - Acute renal failure
  - K-F rings 50% of time
  - Usually cirrhotic

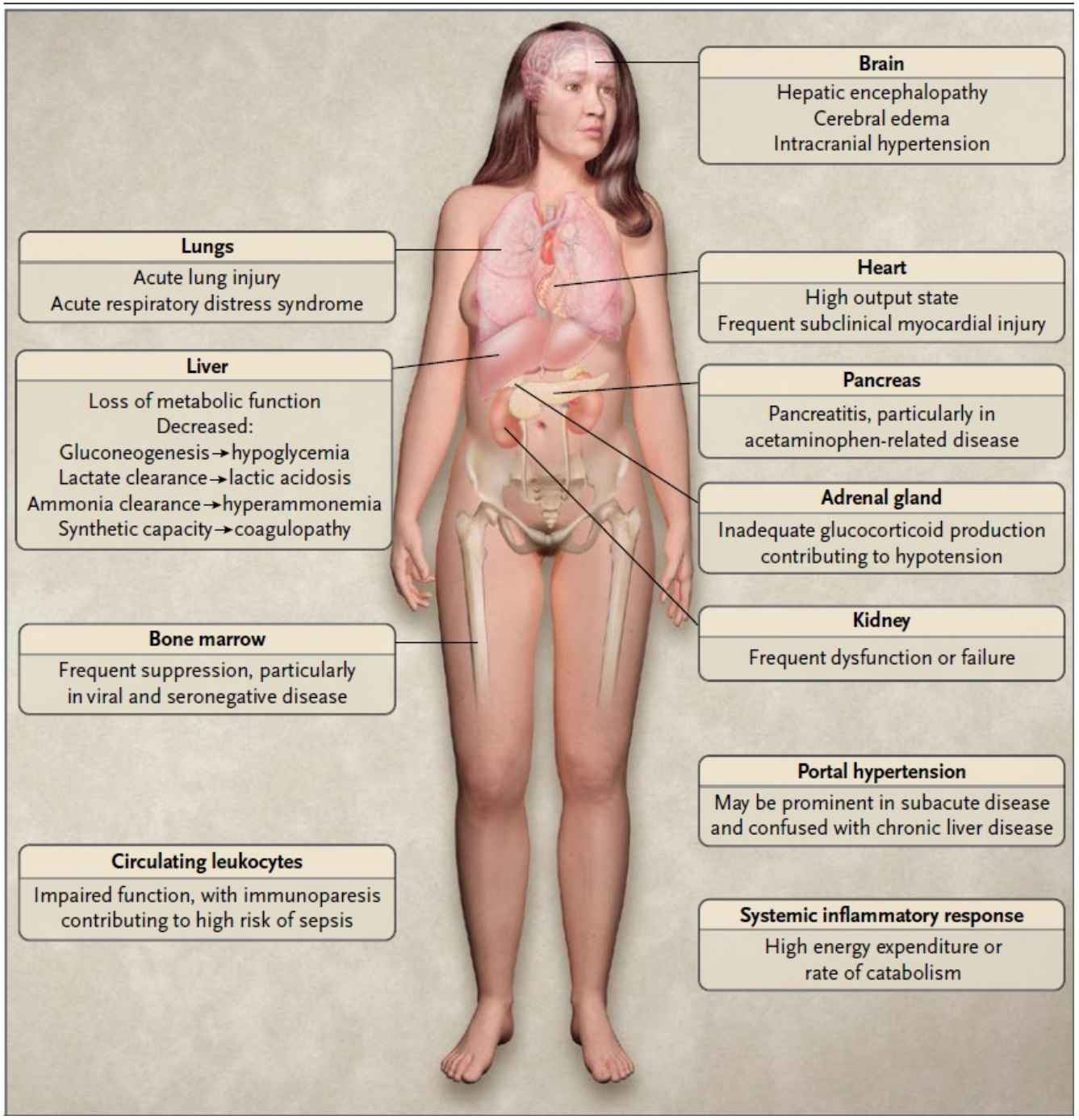
Other Etiologies of ALF

- Toxins
  - Amanita phalloides
  - Organic solvents
  - Herbal supplements
- Metabolic
  - Acute Fatty Liver of Pregnancy
  - Reye's syndrome
- Vascular
  - Shock
  - Budd Chiari syndrome
  - Venoocclusive disease
  - Heat stroke
  - Hepatic Artery Thrombosis
- Other
  - Autoimmune hepatitis
  - Tumor infiltration
  - Primary graft non-function
  - Hemophagocytic Lymphohistiocytosis (HLH)

Pathogenesis of ALF

Massive hepatocyte necrosis and apoptosis:

- Release of cellular contents
- Components of hepatic failure
- Massive cytokine storm
- Hepatocyte regeneration



NEJM 2013; 369: 2526.

Specific ALF Therapies

- N-Acetylcysteine for acetaminophen +/- non-acetaminophen
- Prompt delivery in pregnancy-related ALF (HELLP, AFLP)
- Liver transplantation

- Activated charcoal and high-dose IV penicillin or sibilinin for Amanita mushroom poisoning
- Corticosteroids for autoimmune hepatitis
- Copper chelation, plasmapheresis and antioxidant therapy for Wilson disease
- Lamivudine/Entecavir for HBV
- Acyclovir for HSV
- TIPS/surgical decompression for acute Budd-Chiari
- Hemodynamic support for ischemic liver injury

N-Acetylcysteine for ACM ALF

- Should not be withheld even if ACM ingestions >48 hours prior
- Oral is 1st line therapy with mild encephalopathy
- IV for significant encephalopathy, nausea, hypotension
- NAC administration recommended until firm evidence of improved hepatic function (improved encephalopathy, improving INR, declining transaminases)

Intravenous N-Acetylcysteine Improves Transplant Free Survival in Early Stage Non-Acetaminophen Acute Liver Failure

- Overall survival:
  NAC 70% vs. Placebo 66 % (p=0.283)
- Transplant Free Survival:
  NAC 40% vs. Placebo 27% (p=0.43)
- Transplant Rates:
  NAC 32% vs. Placebo 45% (p=0.09)
- Transplant Free Survival Grade I-II Coma:
  NAC 52 % vs. Placebo 30 % (p=0.010)
- Transplant Free Survival Grade III-IV Coma:
  NAC 9% vs. Placebo 22% (p=0.912)
- Side effects minimal, except nausea/vomiting:
  NAC 14% vs. Placebo 4% (p=0.31)

Gastroenterology 2009; 137: 856-864.

Liver Transplantation

- Each year between 3 and 6% of patients listed for transplant are due to ALF
- Overall ~45% ALF patients listed for transplant → 25% receive transplant
- Patients able to be listed Status 1 for 7 days
- ALF post-OLT: 90% survival 1 month, 70% survival 1 year
- Most diseases do not recur: ACM with repeated overdose, post-OLT AIH

Nonspecific therapies for ALF

- Therapeutic Hypothermia (TH) 32-35º

  (Liver Transplantation 2015; 21: 4-12)

- High Volume Plasma Exchange

  (J Hepatology 2016; 64: 69-78)

- GCSF

  (Gastroenterology 2012; 142: 505).

Nonspecific therapies for ALF

Liver Support Systems:

1) Non-cell based detoxification system:
   Plasmapheresis, plasma exchange, albumin dialysis, charcoal-based hemabsorption
   Prometheus, MARS

2) Cell-based system (incorporate living hepatocytes or hepatic tissue) known as bioartificial liver support systems:
   ELAD, HepatAssist, MELS, AMC BAL
   Differ in cell source, mass, plasma vs. whole blood

- All appear to be safe with some biologic effect
- None FDA approved
- Liver support systems should only be used in context of RCT

Management Of ALF Complications

Leading causes of ALF death: cerebral edema and sepsis

- Hepatic encephalopathy/Hyperammonemia
- Infection prophylaxis
- Sedation and analgesia
- Correction of coagulopathy
- Nutrition
- Circulatory dysfunction
- Cerebral edema
- Assessment of prognosis and need for OLT

Grading of Encephalopathy

1	Mild confusion	Incoordination, Slight tremor
2	Drowsiness	Asterixis, Ataxia, Dysarthria
3	Somnolent but arousable	Hyperreflexia, muscle rigidity
4	Coma	Decerebrate posturing, loss to stimuli

Hepatic Encephalopathy

- Titrate Lactulose dose to avoid intravascular depletion, hypernatremia
- Insufficient data to support use of nonabsorbable antibiotics (ie. Rifaximin)
- Neomycin is contraindicated because of risk of nephrotoxicity
- Grade III/IV encephalopathy → consider intubation

Infection Prophylaxis

- Lung > urinary tract and blood
- Fungal infections in up to 1/3 ALF patients
- Insufficient data to support routine antibiotic prophylaxis in all ALF patients, particularly with early encephalopathy
- Daily surveillance blood cultures and CXR recommended → ALF pts may not exhibit standard infectious signs
- Empiric antibiotics recommended if: surveillance culture with significant isolate, progression or advanced (stage III/IV) encephalopathy, refractory hypotension or presence of SIRS

Sedation and Analgesia

- Psychomotor agitation and pain can increase intracranial pressure
- No data to support particular sedation or analgesia
- Recovery from Propofol short to allow quicker neurologic examination
- Propofol decreases cerebral blood flow which can lower intracranial pressure

Hemostasis

- Spontaneous, clinically significant bleeding is uncommon in ALF patients (<10%)
- Studies with advanced techniques suggest “normal coagulation state”, some patients even hypercoagulable
- Vitamin K 10mg SC or IV x 3 days
- Prophylactic FFP not recommended, INR useful to follow prognosis
- Cryoprecipitate recommended in hypofibrinogenemia (<100 mg/dL)
- Recombinant factor VIIa before high-risk bleeding procedures (biopsy, ICP monitor placement, active bleeding)
- Hemoglobin target for transfusion is 7g/dl
- IV PPI or IV H-2 receptor antagonists shown to reduce risk of GI bleeding in ALF patients (balance risk of VAP)

Nutrition

- ALF is catabolic state (60g/day of protein) - Do Not Protein Restrict
- Enteral nutrition whenever possible
- Higher caloric density feeds may avoid excessive free water → cerebral edema
- Hyperglycemia may exacerbate intracranial hypertension (blood glucose < 150 mg/dl)

Circulatory Dysfunction

- Increased CO, systemic vasodilation, reduced effective central blood volume
- Little evidence supporting use of any specific fluid for volume resuscitation (consider biochemical parameters)
- Albumin has not been investigated in ALF
- Initial pressor recommended is Norepinephrine → Vasopressin

(augment peripheral organ perfusion, preserve splanchnic/hepatic blood flow, minimize tachycardia)

- No mortality studies looking at Hydrocortisone in ALF with vasopressor resistant shock
- Evidence of adrenal dysfunction in > 50% of patients with ALF

Encephalopathy and Cerebral Edema

Grade	Incidence
1	Rare
2	Rare
3	25%
4	75%

Admission Ammonia and Cerebral Edema

- Pathogenesis of cerebral edema incompletely understood
- Hyperammonemia key driver of astrocyte swelling
- Standard ammonia-lowering drugs have not been studied as treatment of cerebral edema in ALF
- Ammonia < 75 μM rarely develops cerebral edema
- Ammonia > 100 μM likely to have high grade encephalopathy
- Ammonia > 200 μM has high risk of cerebral edema

Lancet 2019; 394: 869-881.

Prevent Cerebral Edema

- Cerebral edema most likely in most acute ALF presentations (ACM, ischemia)
- Risk factors: younger age, renal impairment, inotrope support, persistent ammonia > 200 mmol/L
- Head CT and intubation for stage III/IV encephalopathy (consider induction of hypernatremia 145-155)
- No randomized studies to guide indications for ICP monitor placement
- ~50% U.S. centers place ICP monitors in stage III/IV encephalopathy in patients listed for OLT
- Bleeding complications with ICP monitor placement 10-20%

- Quiet environment with limited stimulation
- Head of bed elevated to 30 degrees
- Mild hypothermia (ie. CVVH) should not be treated
- Corticosteroids not useful in cytotoxic cerebral edema
- Severe (>40mm Hg) sustained intracranial hypertension refractory to medical therapy → brainstem herniation and poor neurologic recovery post-OLT
- No data to support empiric use of treatments to reduce ICP

Treat Cerebral Edema

- Cushing's Triad: hypertension, bradycardia, irregular respirations
- Increased muscle tone, hyperreflexia, altered pupillary responses
- Involve neurosurgery early
- Hypertonic saline boluses aiming for serum Na+ 145-155
- Hyperventilation may transiently lower ICP, might delay cerebral herniation
- When ICP >= 25mm Hg for > 10 minutes, first-line Mannitol
- Barbiturate coma (pentobarbital or thiopental) in mannitol refractory cerebral edema

Assessment of Prognosis and Need for Transplant

- Goal: determine who needs OLT, who will get better spontaneously
- Spontaneous recovery more likely with lower grade encephalopathy (grade I-II 65-70%, grade III 40-50%, grade IV < 20%)
- Patients < 10 or > 40 years of age less likely to spontaneously recover
- Etiology an important outcome determinant
- No prognostic criteria adequately sensitive or specific
- King's College Criteria: Sensitivity 61%, Specificity 86%
- MELD > 32: Sensitivity 79%, Specificity 71%
- SOFA (Sequential Organ Failure Assessment) and Clichy criteria

Outcome in ALF

90% have definitive outcome at 3 weeks

Transplant-free survival	45%
Liver Transplantation	25%
Death without transplantation	30%

Etiology and Outcome in ALF

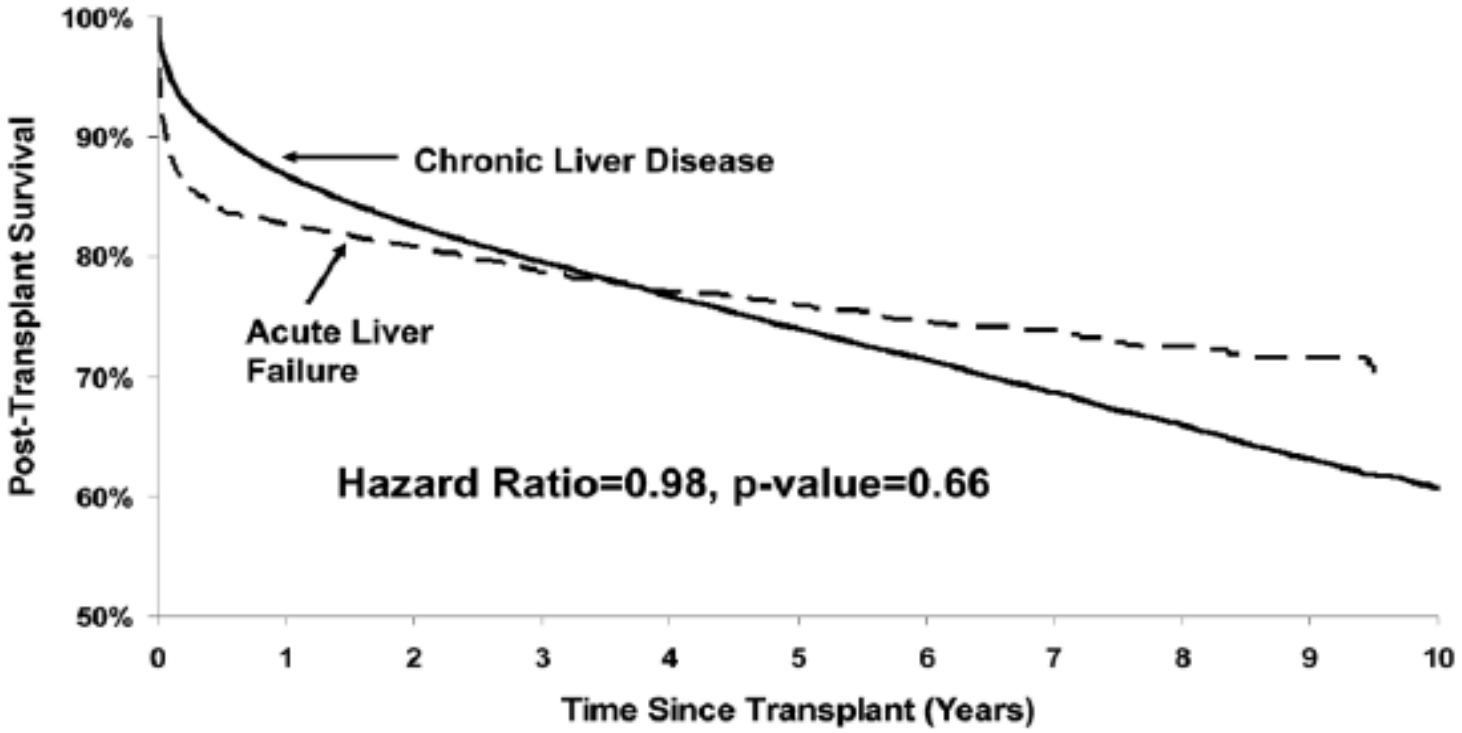
	Acetaminophen	Drugs	Ischemia	Hep A	Hep B	Others
Transplant Free Survival	65%	24%	57%	51%	19%	22%
Transplant	9%	39%	2%	33%	40%	36%
Overall Survival	72%	58%	58%	77%	53%	55%

Liver Transplantation

Why do only 25% receive liver graft?

- Rapidly fatal disease with organ shortage
- No hepatic assist devices FDA approved, unable to bridge to transplant
- Prognosis difficult to assess
- Late presentation can preclude listing
- Some patients not transplant candidates

ALF Post Transplantation



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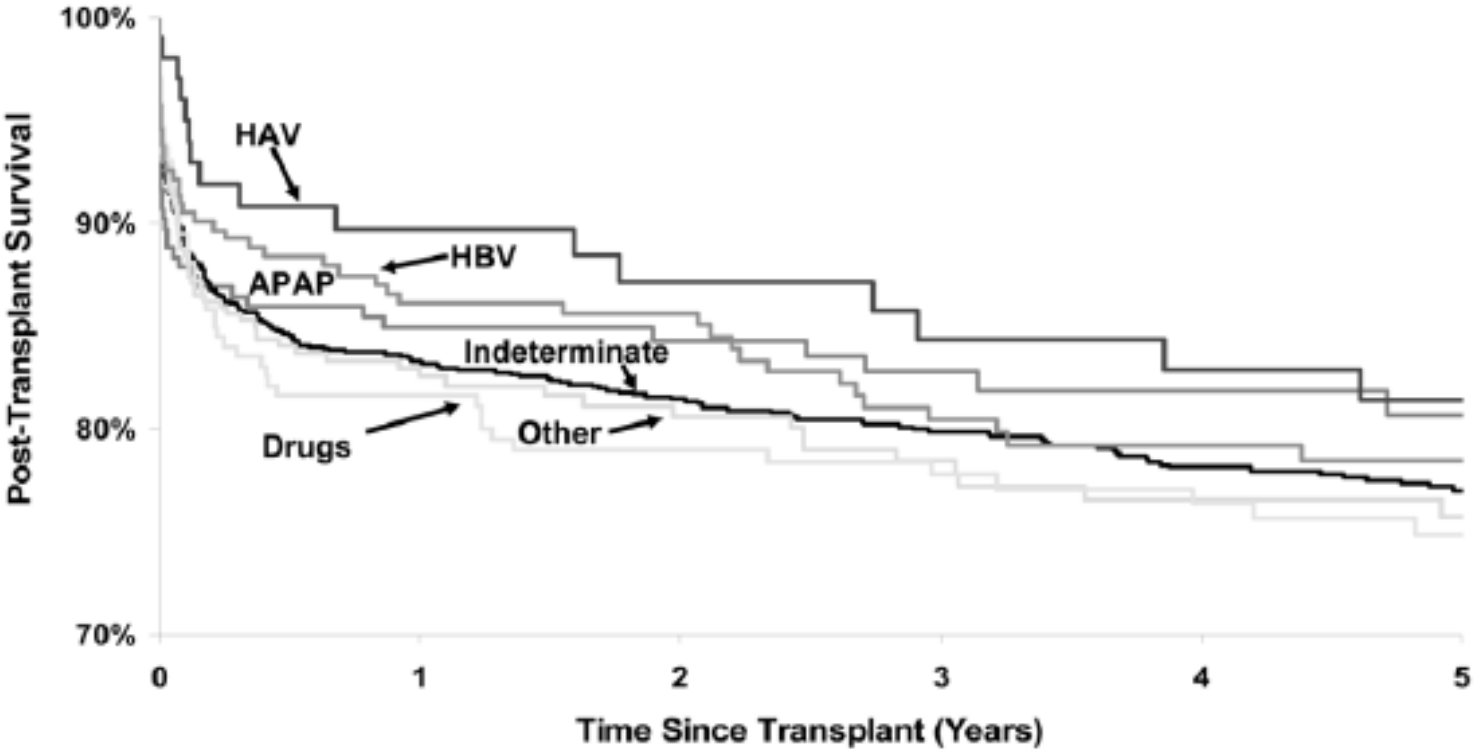
ALF Post Transplantation



Hepatology 2008; 47: 1401-1415

SUMMARY

- Coagulopathy, encephalopathy onset < 26 weeks
- Acetaminophen + Drug > 50% etiology of ALF in U.S.
- Good prognosis: Acetaminophen, HAV, Ischemia
- Poor prognosis: Drug, Indeterminate, HBV, Wilson
- Liver transplantation has improved ALF survival
- Overall 45% patients survive without transplant
- IV NAC proven benefit in all etiologies of ALF
- Worse admission coma grade portends worse prognosis
- Limited effective clinical prognostic markers in ALF, etiology often most helpful

Question

Of the below etiologies of ALF, which has the best likelihood of transplant-free survival:

a) Viral hepatitis B

b) Drug induced liver injury

c) Unintentional acetaminophen overdose

d) Wilson Disease

Answer

Of the below etiologies of ALF, which has the best likelihood of transplant-free survival:

A) Viral hepatitis B

B) Drug induced liver injury

C) Unintentional acetaminophen overdose

D) Wilson Disease

Note: Acute liver failure due to acetaminophen overdose (either intentional or unintentional) has a transplant-free survival of ~65%. Transplant free survival for ALF due to DILI is ~24%, hepatitis B is ~19% and Wilson disease is <20%,

SELECT REFERENCES

Bernal W et al. Acute Liver Failure. NEJM 2013; 369: 2525-34.

Flamm SL et al. American Gastroenterological Association Institute Guidelines for the Diagnosis and Management of Acute Liver Failure. Gastroenterology 2017; 152: 644-647.

Lee WM et al. IV N-acetylcysteine improves transplant-free survival in early-stage non-acetaminophen acute liver failure. Gastroenterology 2009; 137: 856-864.

Seetharan A. Intensive Care Management of Acute Liver Failure: Considerations While Awaiting Liver Transplantation. Journal of Clinical and Translational Hepatology 2019; 7: 384-391.

Stravitz RT et al. Intensive care of patients with acute liver failure: recommendations of the U.S. ALFSG. Crit Care Med 2007; 35: 2498-2508.

Stravitz RT, Lee WM. Acute Liver Failure. Lancet 2019; 394: 869-881.

Wendon J et al. EASL Clinal Practical Guidelines on management of acute liver failure. Journal of Hepatology 2017; 66: 1047-1081.