Acute Liver Failure

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OUTLINE

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

Acute Liver Failure*

Most reliable defining markers:

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

*Distinct from Acute Liver Injury (ALI) and Acute on Chronic Liver Failure (ACLF)

ALF vs. ACLF

	ALF	ACLF
Age	Younger	Older
Chronic liver disease	Absent	Present Signs of portal hypertension
Precipitating factors (by frequency)	DILI, viral hepatitis, autoimmune hepatitis	Infection, alcohol, GI bleeding,
Clinical signs	Liver injury, INR>1.5, HE	Coagulopathy, elevated bilirubin, shock, multiorgan dysfunction
Liver biopsy	Necrosis and collapse	Fibrosis
CNS	Increased intracranial pressure Use CRRT early for HE	HE responds to lactulose/Rifaximin
Infection	Late (<5 d)	Early (<5 d)
Renal failure	Hypoperfusion, ATN	HRS-AKI
Respiratory	ARDS rare	ARDS common
Liver transplantation	KCC, MELD Status 1A listing	MELD No priority in MELD system

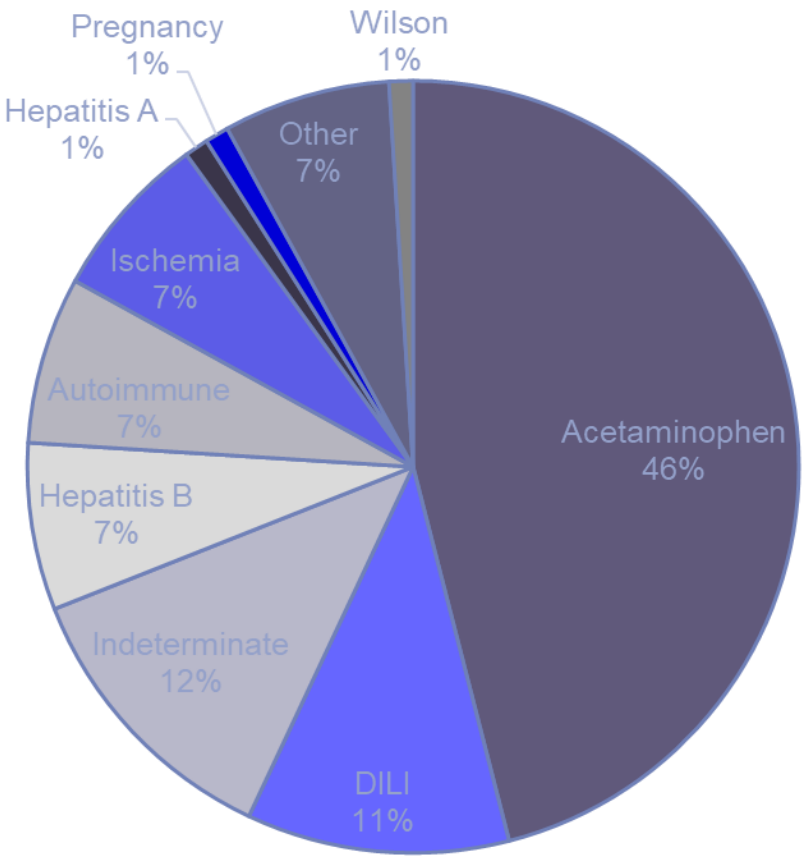
ACLF, acute on chronic liver failure; ALF, acute liver failure; ARDS, acute respiratory distress syndrome; ATN, acute tubular necrosis; CNS, central nervous system; CRRT, continuous renal replacement therapy; DILI, drug-induced liver injury; GI, gastrointestinal; HE, hepatic encephalopathy; HRS-AKI, hepatorenal syndrome-acute kidney injury; INR, international normalized ratio; KCC, King's College Criteria; MELD, Model for End-Stage Liver Disease.

American Journal of Gastro 2023; 1134.

Background on ALF

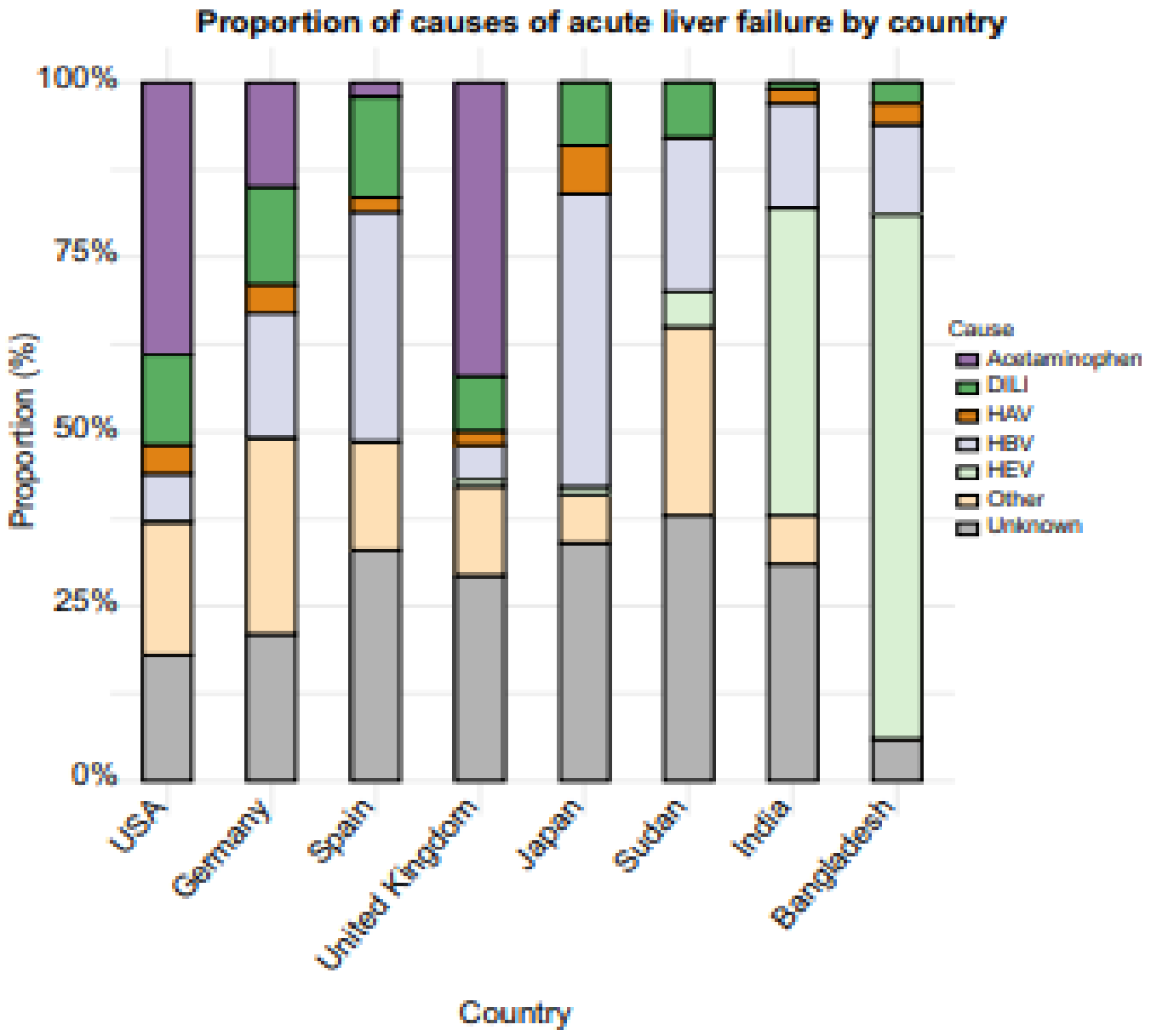
- Rare: ~2-3,000 cases/year in U.S.
- All patients should be cared for in ICU
- No one medical center can study the condition
- Variety of etiologies
- No viable treatment for all patients
- Morbidity/mortality 94% prior to transplant
- Patients can be listed UNOS Status 1A for 7 days
- Prior to 1980's, HBV was >40% cases
- Acute Liver Failure Study Group (ALFSG) est. 1998

Etiology of ALF in Adults in the United States



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

Lancet 2019; 394: 869-881.



JHEP Reports 2024

Etiology and Clinical Characteristics of ALF

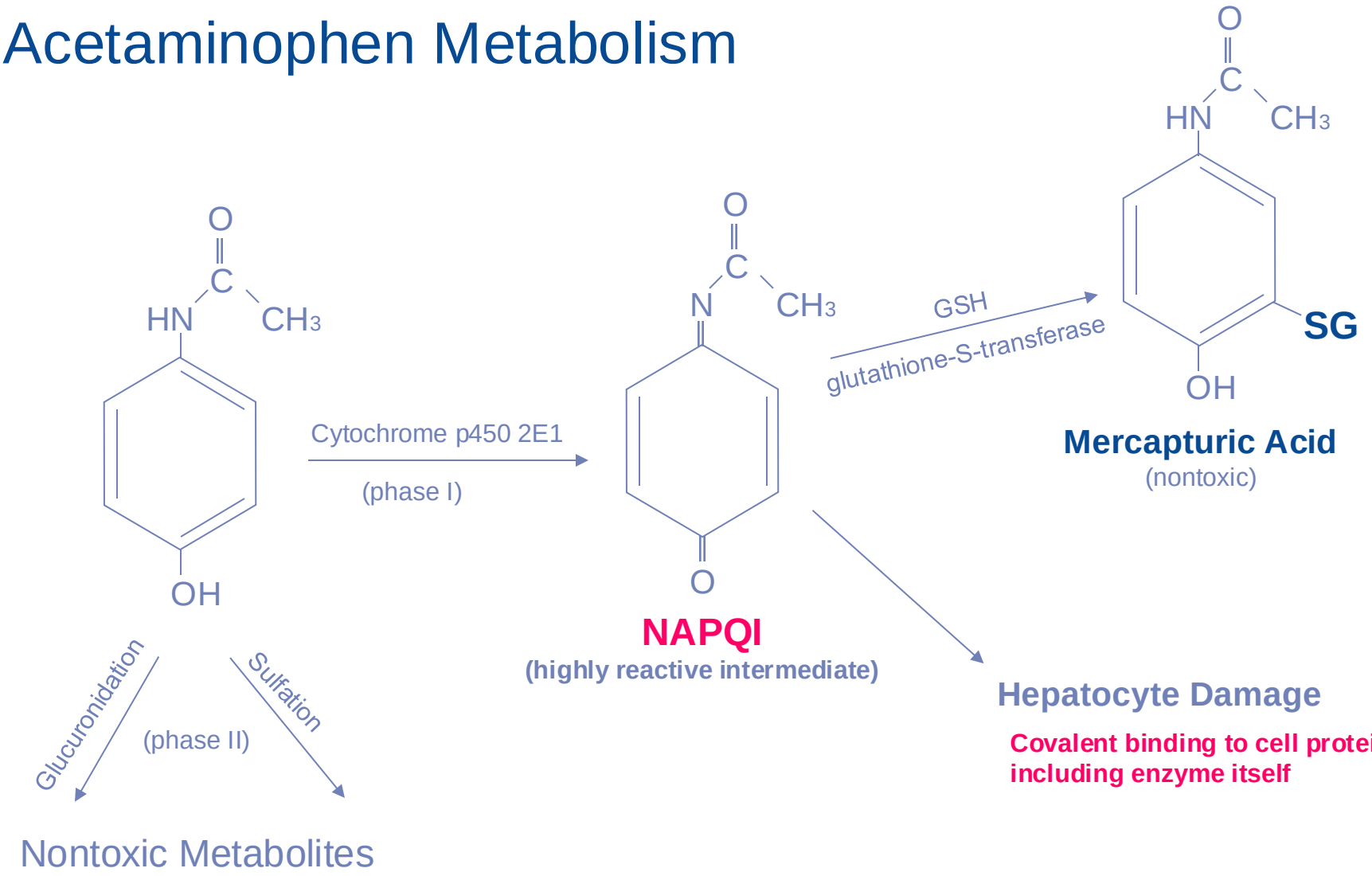
	Acetaminophen	Drugs	Ischemia	Hep A	Hep B	All Others
Median Age	37	47	53	50	45	40
Female Sex	75%	67%	58%	44%	45%	64%
Jaundice to Coma (Days)	1	12	2	4	8	7
Coma ≥ 3	54%	36%	56%	54%	51%	44%
Median ALT	3780	654	2311	2229	1410	758
Median Bilirubin	4.3	19.6	3.8	12.0	19.2	17.2
Transplant Free Survival	65%	24%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

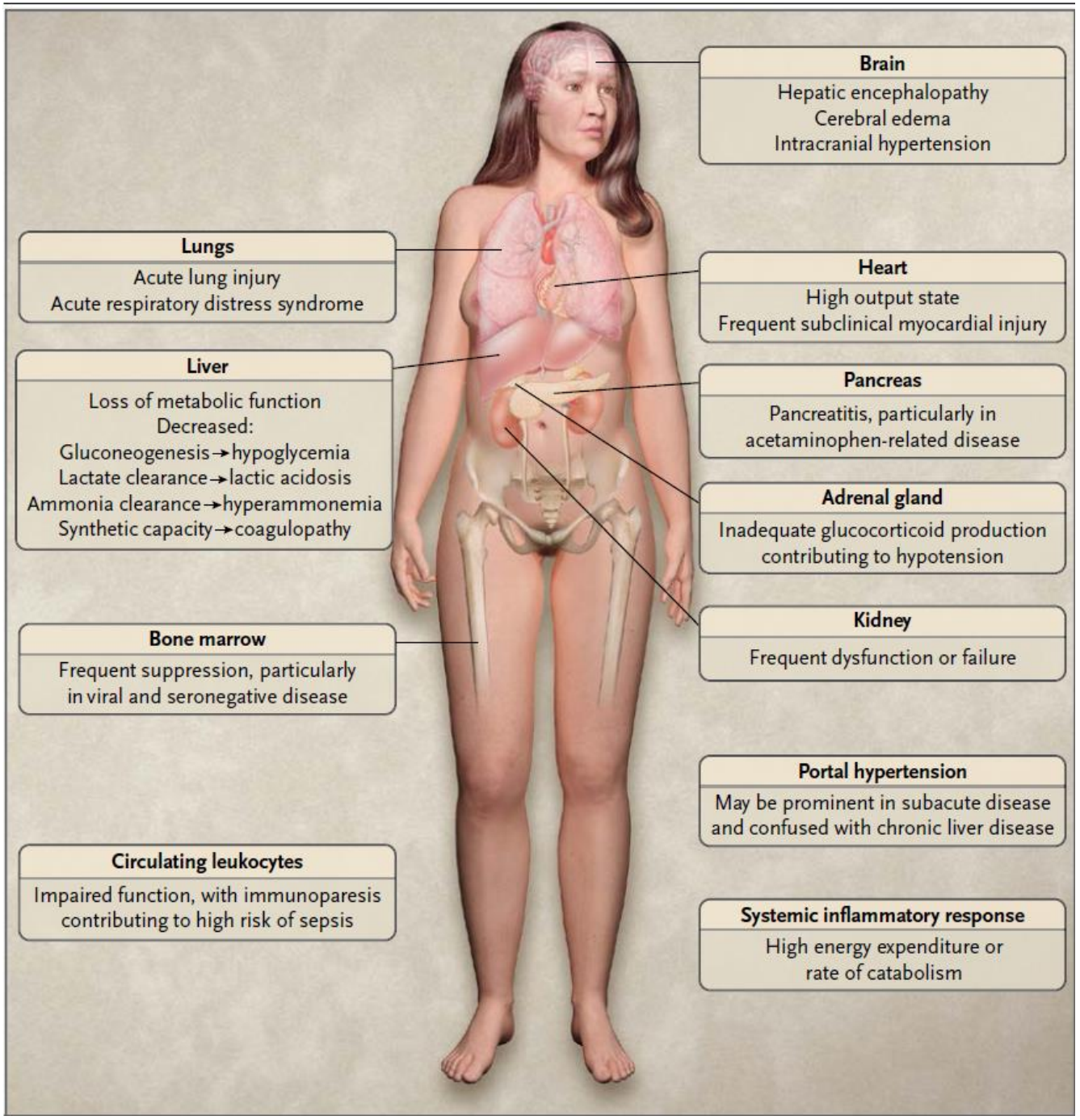
Other Etiologies of ALF

- 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 (IL-6, TNF-α, HGF)
- 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
- IV Corticosteroids for autoimmune hepatitis
- Hemofiltration plasma exchange for Wilson disease
- Nucleoside analog (Entecavir, Tenofovir) for HBV
- Acyclovir for HSV or VZV
- Anticoagulation, TIPS, revascularization (stent/angioplasty) for 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: Status 1A

- Each year 3-5% of liver transplants done in US are for ALF
- Candidate is at least 18 years old
- Candidate has life expectancy of < 7 days without a liver transplant
- Onset of encephalopathy within 56 days of first signs or symptoms of liver disease
- No pre-existing diagnosis of liver disease
- Admitted to ICU
- At least one of following:
  - Ventilator dependent
  - Requires dialysis (CVVH or CVVHD)
  - INR > 2.0

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

Management of Encephalopathy in ALF

1	Trivial lack of awareness Shortened attention span Impairment of addition or subtraction Altered sleep rhythm	• Contact transplant center • Obtain baseline head CT
2	Lethargy or apathy Disorientation for time Obvious personality change Inappropriate behavior Dyspraxia Asterixis	• Transfer to ICU • Neuro checks q1 hour
3	Somnolence to stupor Responsive to stimuli Confusion Gross disorientation Bizarre behavior	• Intubation if appropriate • Repeat head CT • Avoid opioids and benzos for sedation • Consider propofol
4	Coma	• Repeat head CT • Consider ICP monitor if transplant candidate • Initiate treatment for cerebral edema

American Journal of Gastro 2023: 1135.

Management of Encephalopathy in ALF

- Continuous renal replacement therapy (CRRT) can effectively lower ammonia in patients with ALF
- CRRT lowering of ammonia associated with reduced mortality and increased transplant free survival (TFS) at 21 days in ALF
- Ornithine phenylacetate use not recommended in ALF
- Rifaximin + Lactulose more effective than Lactulose alone in managing encephalopathy in chronic liver disease
- Extrapolating from chronic liver disease, Rifaximin is often used in ALF though data not available
- Grade III/IV encephalopathy → consider intubation, stop Lactulose

Infection Prophylaxis

- Lung > urinary tract and blood
- Fungal infections in up to 1/3 ALF patients
- No improvement in rate of bloodstream infection or 21-day mortality with prophylactic antimicrobials → not recommended in ALF
- Regular surveillance cultures and CXR recommended (frequency less clear) → 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 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

West Haven 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 independent risk factor for high grade encephalopathy
- Ammonia > 200 μM predicts 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 65-69%, Specificity 82-93%
- MELD > 32: Sensitivity 74%, Specificity 67%
- Clichy criteria
- Escudie criteria (mushroom) and Swansea criteria (AFLP)

Outcome in ALF

90% have definitive outcome at 3 weeks

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

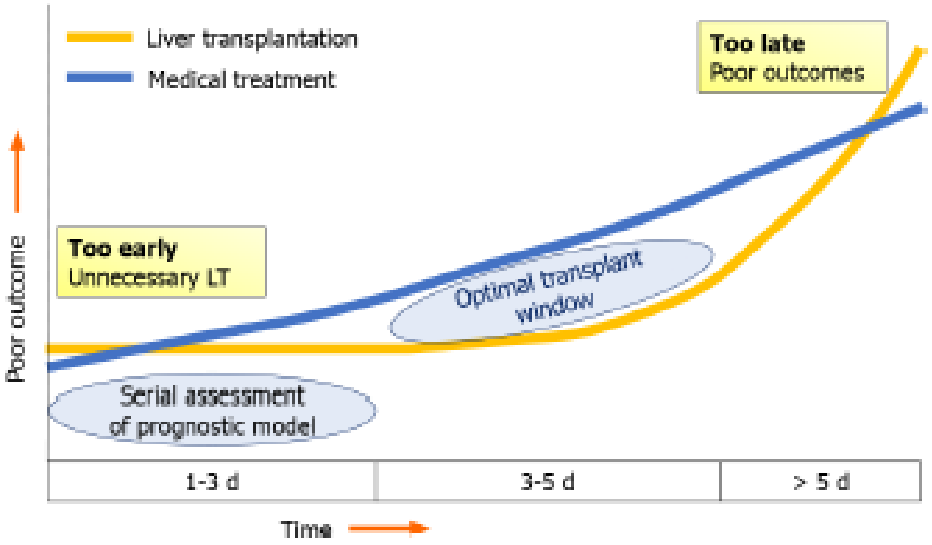
Etiology and Outcome in ALF

	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%

Complexities of LT for ALF

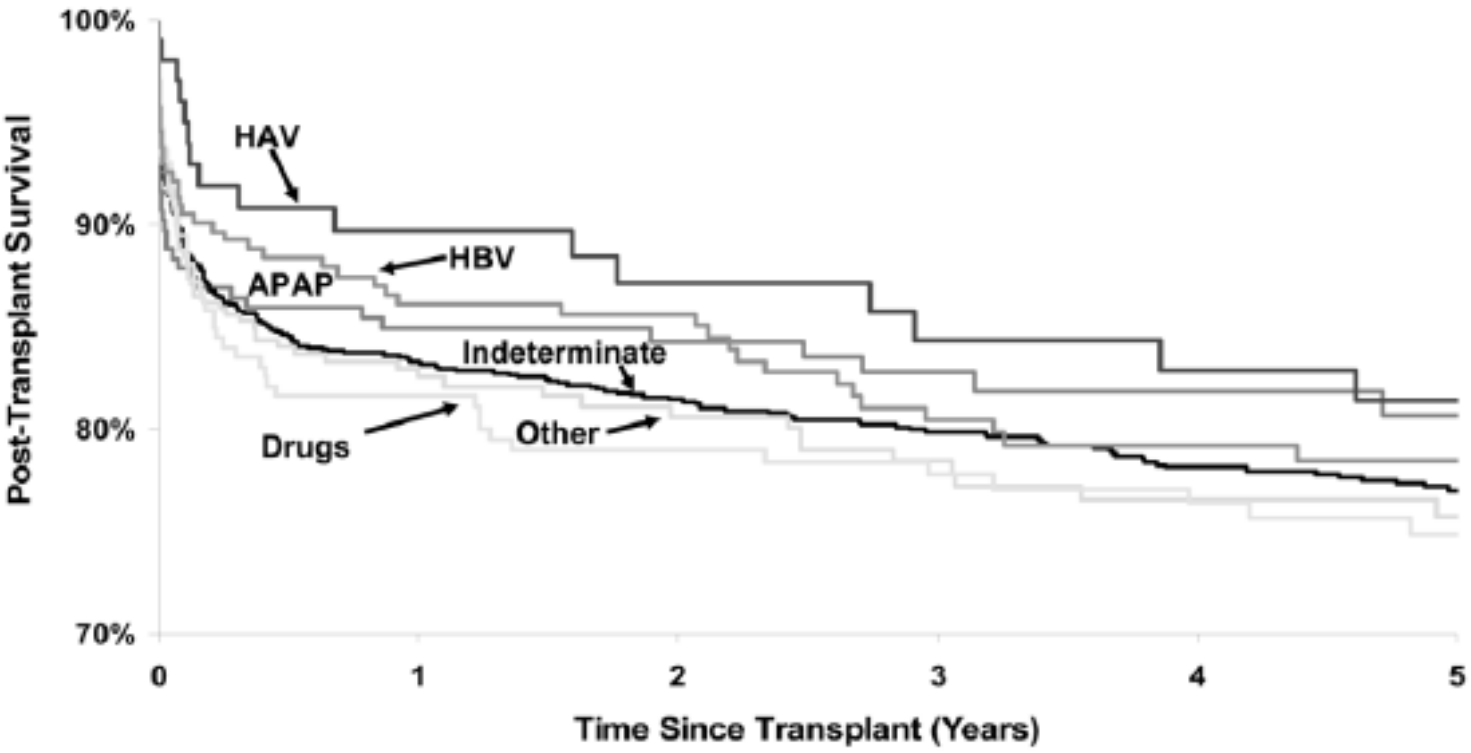
- Lack of helpful prognostic models
- Rapidly progressive disease (Acetaminophen)
- Time constraints for pre-transplant evaluation
- Development of complications on waiting list
- Graft shortage
- Unnecessary transplantation
- No consensus on delisting criteria for too sick
- Inability to bridge to liver transplant
- Living donor liver transplantation

Complexities of LT for ALF



World Journal of Transplantation 2021; 11: 187-202.

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 and progress in ICU care have improved ALF survival in last 10 years
- 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
- Narrow window for liver transplantation in ALF, particularly acetaminophen

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