Acute (Fulminant) Liver Failure

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Definitions

- ***Classic:*** Development of hepatic encephalopathy within 8 weeks* of initiation of *symptoms* in a patient without **known** chronic liver disease.
  - Patients with Acute Onset AIH, Budd-Chiari, or Wilson disease qualify even in the presence of fibrosis.
- ***Practical:*** Development of:
  - hepatic encephalopathy and coagulopathy (INR > 1.5)
  - within 26 weeks* from the onset of *jaundice*,
  - in patient without known chronic liver disease.
- Patients who develop coagulopathy, but no hepatic encephalopathy have "Acute Liver Injury"

* For "Status 1" transplant listing </= 8 weeks or 56 days)

Grades of Hepatic Encephalopathy (Porto-Systemic Encephalopathy – PSE)

- **Grade I**:
  - Inverse sleep pattern, personality change, slight change in mental status. (GCS=14-15)
  - Normal EEG.
- **Grade II**:
  - Confusion, drowsiness, asterixis. (GCS=11-13)
  - Abnormal EEG with generalized slowing.
- **Grade III**:
  - Incoherence, stupor, agitation. (GCS=8-10)
  - Abnormal EEG.
- **Grade IV**:
  - Unresponsiveness, coma, decerebrate posturing, seizures, areflexia. (GCS<8)
  - Abnormal EEG.

Incidence

- ***Incidence***:
  - 2300-2800/ year in USA;
  - 6% of adult transplants;
  - 6% of liver-related deaths;
  - 0.1% of deaths in USA.

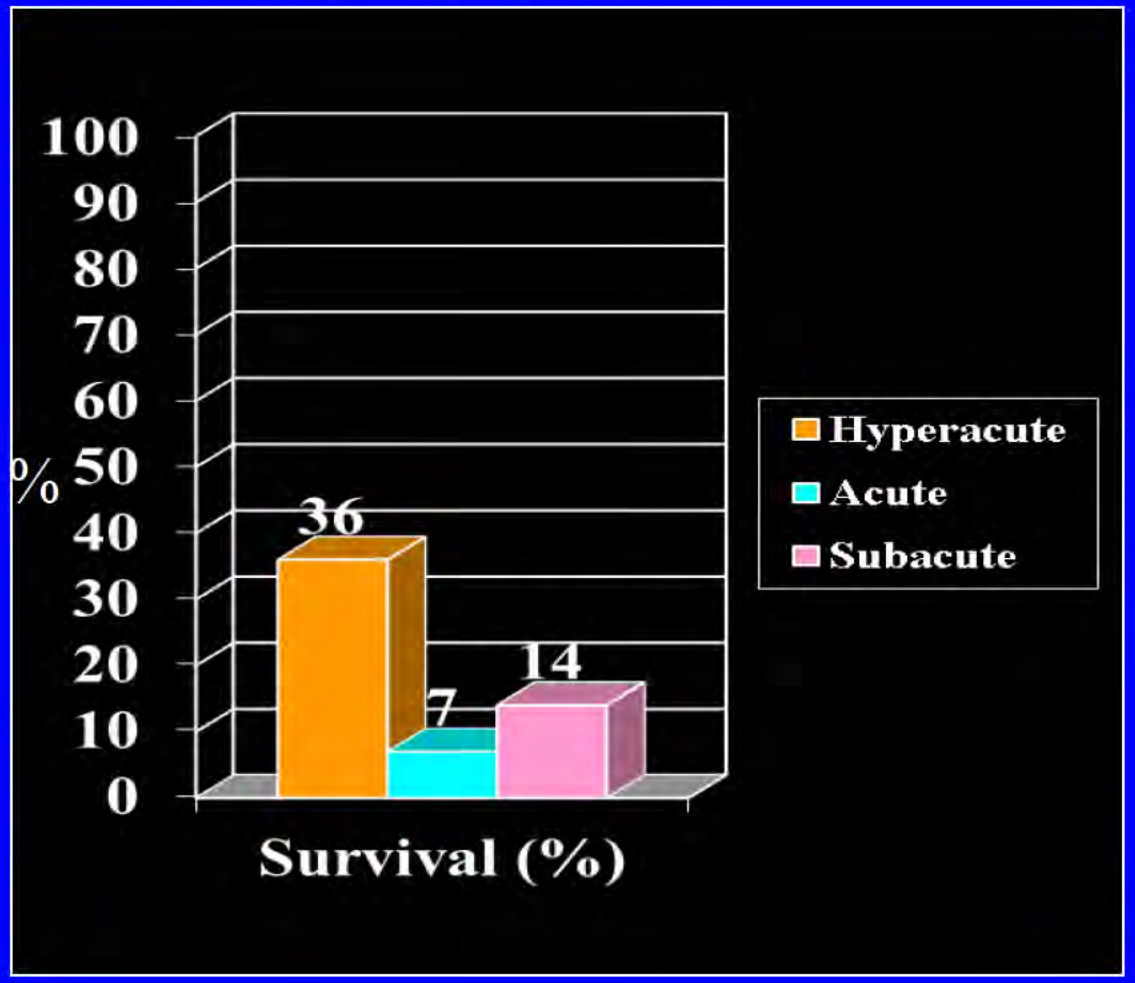
Factors Affecting Survival in FHF

- Acuteness of illness
- Etiology
- Brain Edema/ Intracranial Hypertension
- Acute Kidney Injury
- Superimposed Infection (bacterial or fungal)

Acuteness of Illness

Subtypes of Acute Hepatic Failure

- ***Hyperacute***:
  Clinical encephalopathy in **< 8 days** ***from jaundice*** *(acetaminophen, mushrooms, ecstasy heat shock, heat shock and ischemia)*.
- ***Acute:***
  Clinical encephalopathy **8 – 28 days** ***from onset of jaundice*** *(viral, pregnancy, vascular)*
- ***Subacute:***
  Minimal encephalopathy from **29 days to 26 weeks** after ***onset of jaundice*** *(DILI, unknown)*
  -clinical picture may mimic cirrhosis



Impact on Survival:

Etiology
and
Brain Edema/ Intracranial Hypertension
and
Acute Kidney Injury

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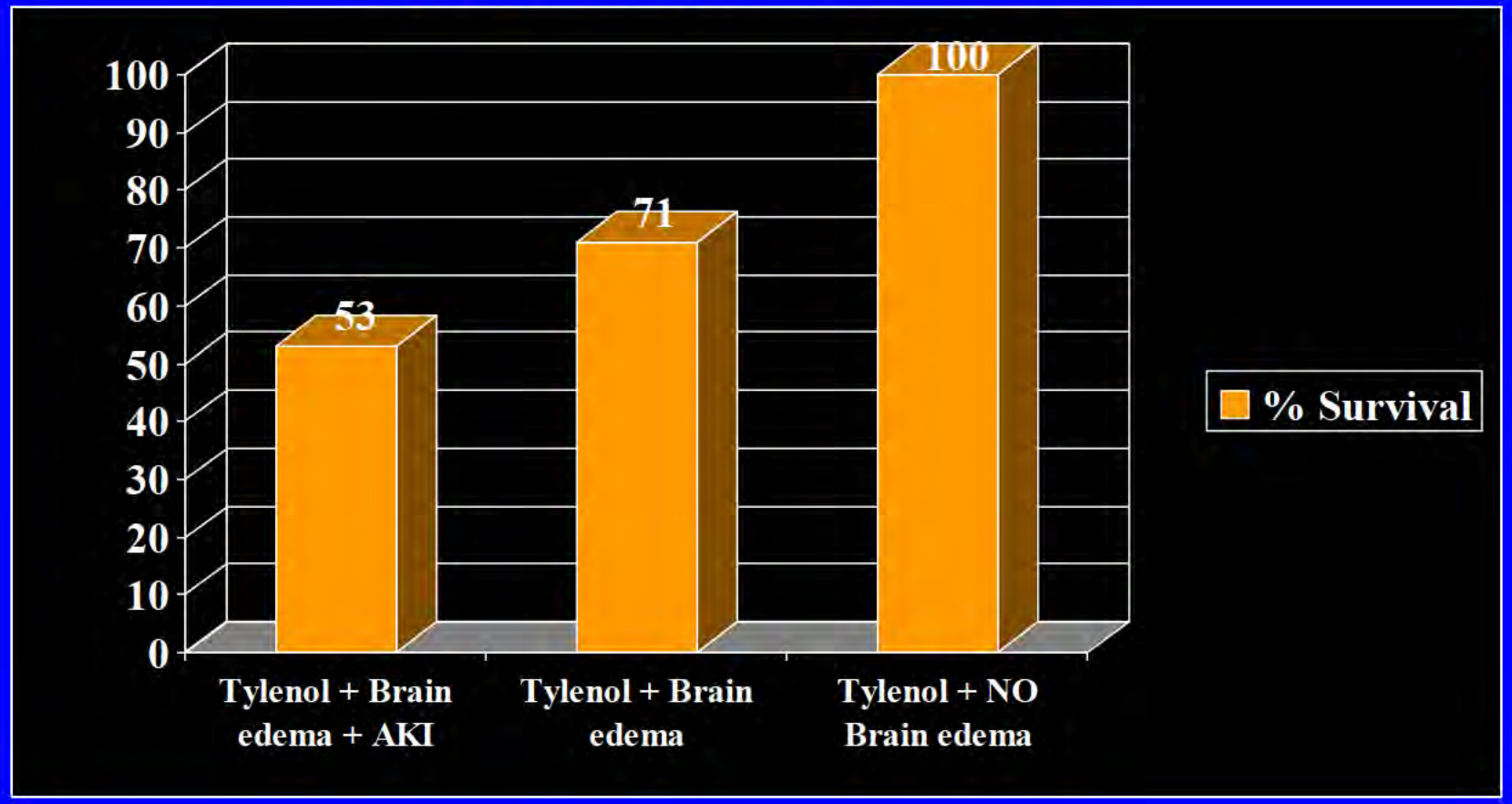
Expected Survival by Etiology, Brain Edema & AKI
ACETAMINOPHEN



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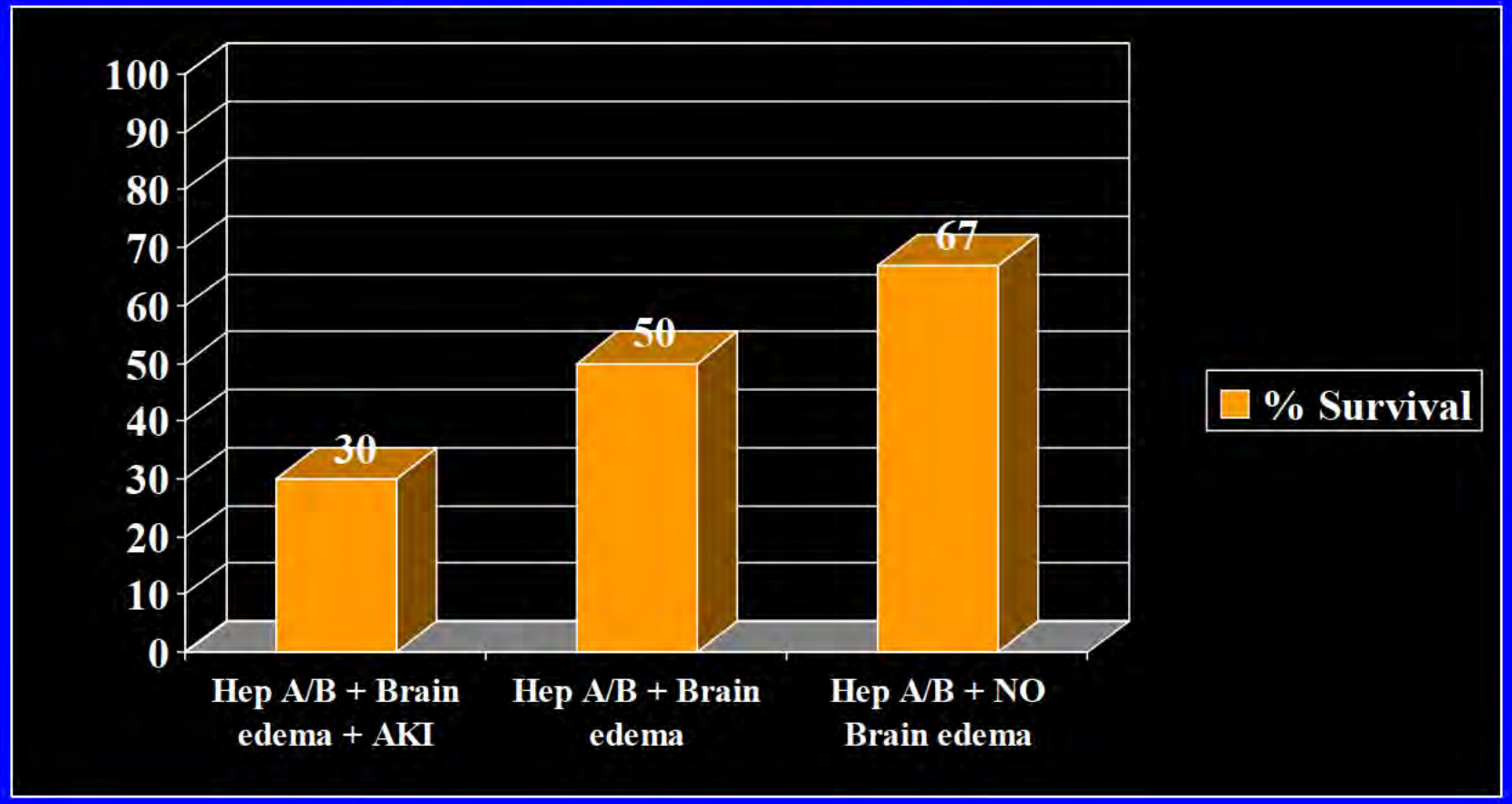
Expected Survival by Etiology, Brain Edema & AKI

Hepatitis A or Hepatitis B



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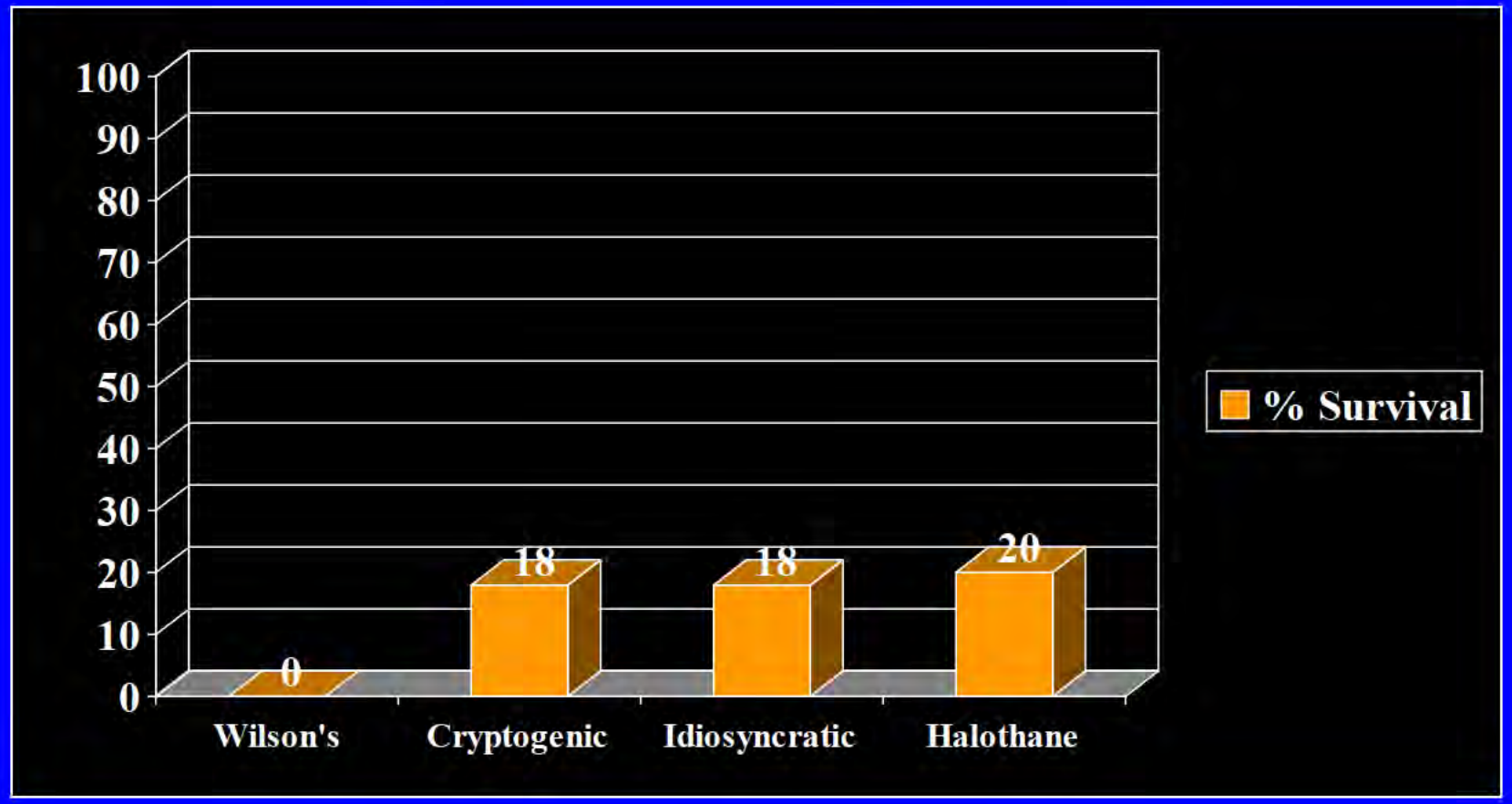
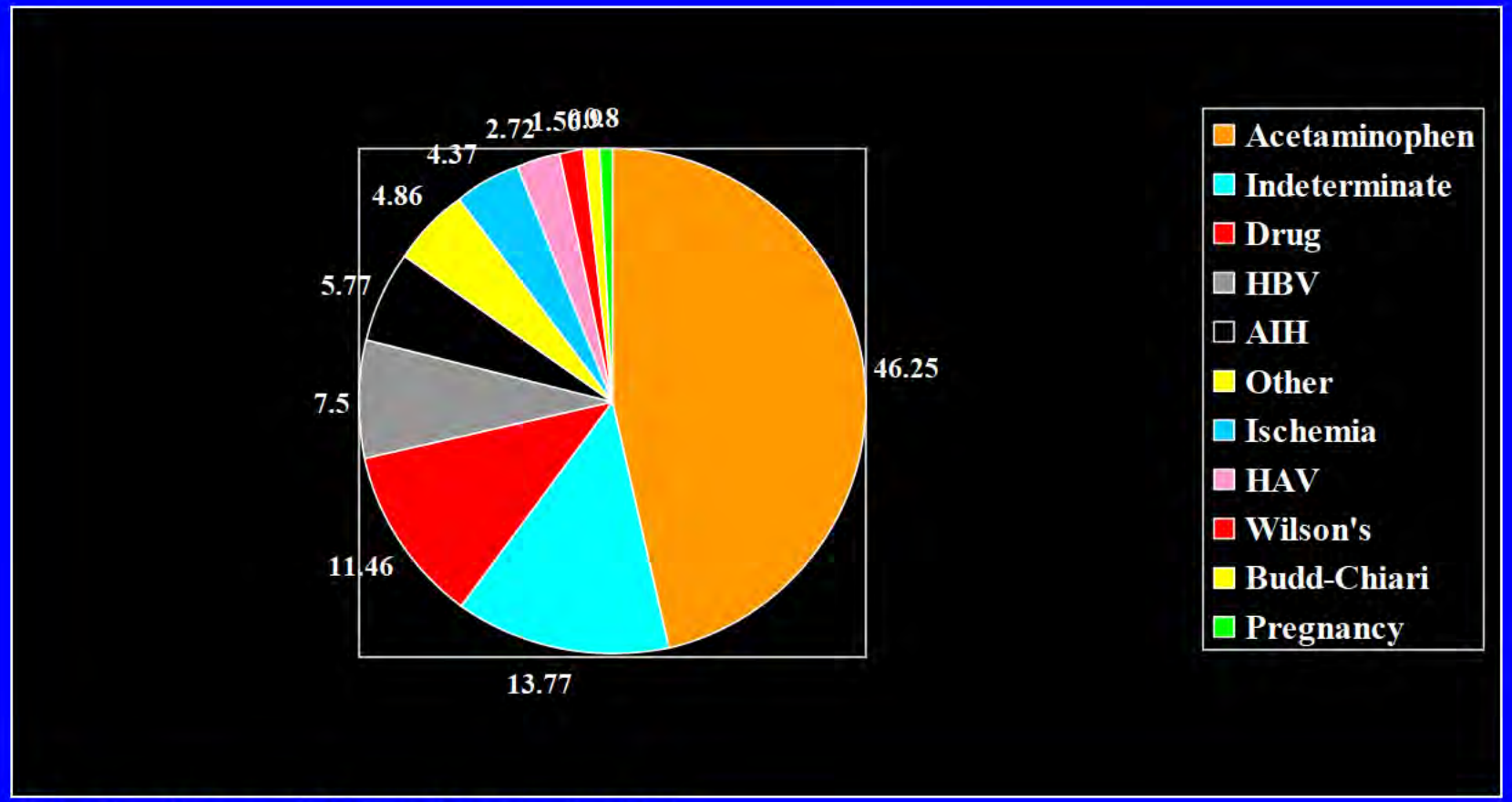
Expected Survival by Etiology



Causes of Fulminant Hepatic Failure

Etiology of Acute Liver Failure 1998-2007



Best Practice & Research Clinical Gastroenterology
Volume 26, Issue 1, February 2012, Pages 3–16

Causes of FHF

Viral Infection

- Hepatitis A
- Hepatitis B +/- HDV
- Hepatitis E
- Hepatitis C (very rare)

- Herpes Simplex
- Cytomegalovirus
- Varicella-Zoster
- Epstein-Barr virus
- Paramyxovirus
- Adenovirus (41F)
- Dengue
- Hemorrhagic Fever
  - Yellow Fever,
  - Ebola,
  - Marburg,
  - Lassa,
  - Rift Valley

Causes of FHF

Drugs & Toxins

- **DOSE RELATED**
  - Acetaminophen
  - CCl_4
  - Amanita Poisoning (A. phalloides, A. ocreata, A. bisporigera, A. virosa, Galerinas, Lepiotas)
  - Yellow phosphorus
  - Bacillus cereus toxin

ISCHEMIA RELATED

- Long-acting Niacin
- Cocaine
- Methamphetamine

IDIOSYNCRATIC

Causes of FHF

Drugs - Idiosyncratic

- **Amoxicillin-clavulanate**
- Allopurinol
- Amiodarone
- Amphetamines
- Dapsone
- Diclofenac
- Didanoside
- Disulfiram
- Ecstasy
- Efavirenz
- Etoposide
- Flutamide
- Gemtuzumab
- Halothane
- Imipramine
- Isoflurane
- Isoniazid
- Ketoconazole

Causes of FHF

Drugs - Idiosyncratic

- Labetalol
- Lisinopril
- Metformin
- Methyldopa
- Nefazodone
- Nicotinic acid
- Ofloxacine
- Phenytoin
- Pirazinamide
- Propylthiouracil
- Quetiapine
- Rifampin-INH
- Statins
- Sulfonamides
- Tolcapone
- Trimethoprim-Sulfametox
- Troglitazone
- Valproic acid

Causes of FHF

Herbals & Supplements

- Chaparral (Larrea tridentata)
- Comfrey (Symphytum officinale L)
- Germander (Teucrium chamaedrys)
- Greater celandine (chelidonium majus)
- Green tea extract (Camellia sinensis)
- Gum Thistle (Atractylis gummifera L)
- He Shon Wu (Polygonum multiflorum)
- Heliotrope (Heliotropium popovii and H. lasiocarpum)
- Huamanripa (Senecio tephrosioides)
- Impila (Callilepis laureola)
- Kava kava (Piper metysticum)
- Ma Huang (Ephedra sinica)
- Pennyroyal (Mentha pulegium)
- Rattleweed (Crotalaria retusa)
- Senecio (Senecio vulgaris)
- Skullcap (Scutellaria lateriflora)
- Sunnhemp (Crotalaria juncea)
- Bai-Fang herbs®
- Herbalife ®
- Hydroxycut ®(has green tea extract)
- Jin Bu Huan®
- LipoKinetix®

Causes of FHF

Metabolic & Pregnancy-related

- ***METABOLIC***
  - Wilson's Disease
  - Alpha-1-antitrypsin
  - Galactosemia
  - Tyrosinemia
  - Fructose Intolerance
  - Neonatal Fe storage dz

- ***PREGNANCY-RELATED***
  - Acute fatty liver
  - HELLP Syndrome (**H**emolysis, **E**levated **L**iver function, **L**ow **P**latelets)

Causes of FHF

Neoplastic & Miscellaneous

- ***MISCELLANEOUS***
  - Autoimmune hepatitis
  - Budd-Chiari
  - Veno-occlusive/ SOS
  - Shock Liver & CHF
  - Heat Stroke
  - Adult-onset Still's disease
  - Reye's syndrome

- ***NEOPLASTIC***
  - Lymphoma
  - Liver Metastasis (breast, small cell lung cancer, melanoma)

- ***CRYPTOGENIC***

Primary and Secondary Causes of ALF

Need for Transplantation

EASL GUIDELINES; Journal of Hepatology 2017 vol. 66 j 1047–1081

Disease Group	Hepatic Primary ALF Liver Transplant may be option	Extrahepatic Secondary ALF and Acute on Chronic LF Liver Transplant is NOT likely option
Acute Liver Failure	-DILI -Viral Hepatitis -Toxin -Budd-Chiari -Autoimmune -Pregnancy related	-Ischemic Hepatitis -Systemic Disease: -Infiltrative Disease -Metabolic Disease -Lymphoma -Infection (malaria) -Hemophagocytic Syndrome
Chronic disease with ALF Phenotype	-Fulminant Wilson -Acute onset AIH -Budd-Chiari -HBV reactivation -Selected Alcoholic Hepatitis	-Liver resection for primary or metastatic Cancer. -Alcoholic Hepatitis (most cases)

Etiologic & Management Work-Up

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Etiologic work-up

- Establish day of onset of jaundice.
- Travel History (exotic viruses)
- Medication (Rp & OTC), drug/alcohol, CAM therapies, environmental & food exposures.
- Sexual history, piercing, tattooing, …
- Family history (Wilson's, alpha-1-antitrypsin,…)
- Stigmata of chronic liver disease.
- Mushroom ingestion with severe gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal cramping), which occur within hours to a day of ingestion

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Etiologic work-up

- **HAV** anti-HA IgM
- **HBV** anti-HBc IgM, HBV-DNA
- **HCV** HCV-RNA , anti-HCV
- **HDV** anti-HD IgG, HDV-RNA
- **HEV** anti-HE IgM, HEV-RNA
- **CMV** CMV-DNA quant, anti CMV IgG & IgM
- **HSV** anti-HSV IgG & IgM, HSV PCR
- **EBV** acute serology, PCR
- **VZV** Serology, PCR
- **Parvovirus** PCR
- **Drug/Toxin** History, toxicology drug screen
- **Adenovirus** PCR in whole blood

- **Wilson's** 24h urine Cu >100mg/dL, copper, ceruloplasmin <20 mg/dL, K-F rings, Coombs (DAT) test negative **[alk.phos/bili <4 (sn 94%,sp 96%) & AST/ALT >2.2] (sn 100%,sp 100% if both true; Hepatology. 2008 Oct;48(4):1167-74)** , low uric acid, (total & free Cu)
- **Autoimmune** ANA, anti-LKM, anti-SLA, ASMA, anti-LC, QIG's, LIVER Bx if suspected & Ab(-)
- **AFLP** Pregnancy +/- pre-eclampsia, ALT<500
- **Budd-Chiari** U/S+Doppler, angio-CT
- **Ischemia** Hx.of shock or CHF; Echocardiogram

Standard Tests

- CBC with diff., PT/INR
- Blood type & screen done twice (two separate samples)
- Pregnancy test (females)
- CMP, Phosphorus, Mg, CK.
- Amylase, lipase
- Daily arterial ammonia (intra-cranial HTN rare if < 75 mcMol)
- AFP on day 1, day 3, and day of 1st decrease of ALT.
- Acetaminophen level; acetaminophen adducts when available.
- Arterial blood gas
- Arterial Lactate
- HIV status (rapid test)
- Calculate (in Kg):
  - "Predicted (or Ideal) Body Weight" (to manage Tidal Volume, and for High Volume Plasma Exchange)
  - "Lean Body Weight" (to give hypertonic saline)

Management

Preventive Management

- Optimize likelihood of Transplant-free survival:
  - N-acetylcysteine IV up to for 5 days (may affect regeneration)
  - High Volume plasma Exchange.
- Minimize Risk of Brain edema and Intracranial hypertension:
  - Detect & treat Hepatic encephalopathy early (Neuro-check q 1-2 h)
    - Early CVVHDF for hyperammonemia
    - Recognize predictors of intracranial hypertension
  - Keep serum Na of >/= 145 mEq/L (145-**150**)
    - (Na > 150 causes cell damage)
- Prevent hypoglycemia (glucose goal: 110-180 mg/dL)
  - Tube feeding or IV glucose (in normal saline)
  - Close glucose monitoring q 1-2 hours
- Manage Hemodynamic Compromise
- Protect Renal function:
  - Optimize intravascular volume
  - Avoid nephrotoxins
  - Treat Hepatorenal Syndrome early

Preventive Management

- Minimize risk of bleeding:
  - Correct platelets and Fibrinogen for invasive procedures (Thrombo-elastography guided)
  - Monitor & correct extreme coagulopathy (plat < 10K, INR > 7)
  - Proton pump inhibitors **until on enteral nutrition**.
- Minimize risk of infection:
  - Protect airway in grade III and IV hepatic encephalopathy
  - Enteric feeding to minimize bacterial translocation
  - Remove foreign bodies that facilitate infections (IUD, piercings)
- Treat infections early:
  - Surveillance cultures
  - Recognize predictors of current infection
- DVT Prophylaxis:
  - Sequential Compression device

Optimizing Transplant-Free Survival

IV NAC in Non-Acetaminophen ALF

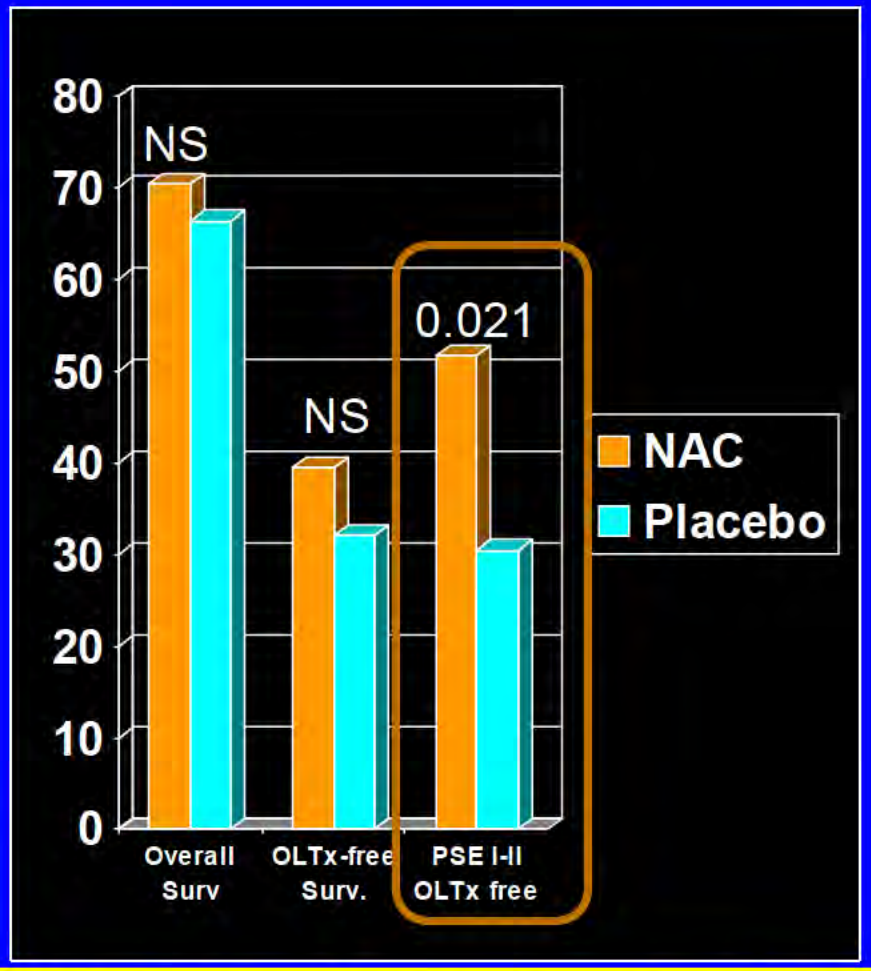
Lee WM et al. Gastroenterology. 2009 Sep;137(3):856-64

- **Patients:**
  - 848 adults screened,
  - 173 qualify and randomized.
- **Stratification:**
  - PSE I-II vs
  - PSE III-IV
- **Intervention:**
  - IV NAC x 150 mg/kg/d x 72h (82 pts) vs
  - Placebo (92 pts).

- **End point:**
  - 1: survival,
  - 2: OLTx free survival.
- **Etiology:**
  - Drug 26%,
  - Indeterminate 24%,
  - HBV 21%,
  - AIH 15%,
  - Other 14%.

IV NAC in Non-Acetaminophen ALF

Lee WM et al. Gastroenterology. 2009 Sep;137(3):856-64



CONCLUSION: In Early Non-Acetaminophen ALF, NAC improves Spontaneous Survival

High-volume plasma exchange (HVPE) in patients with acute liver failure:
An open randomized controlled trial

Larsen FS et al. Journal of Hepatology, 2016-01-01, Volume 64, Issue 1, Pages 69-78

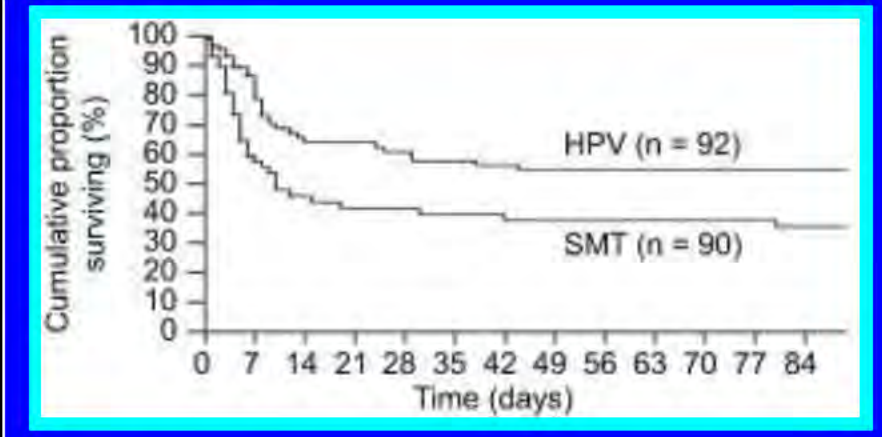
- Prospective, randomized, controlled, multicenter trial
- 182 patients with ALF: standard medical therapy (SMT; 90 patients) or SMT plus High-Volume Plasma Exchange (HVPE; 92 patients) x 3 consecutive days.
- The baseline characteristics of the groups were similar.
- Primary endpoint: liver transplantation-free survival during hospital stay.
- Secondary-endpoints: survival after liver transplantation (ITT analysis).
- **RESULTS**:
- Hospital survival was **58.7**% with HVPE *vs.* **47.8**% for control group (hazard ratio (HR), with stratification for liver transplantation: 0.56; 95% confidence interval (CI), 0.36–0.86; $p = 0.0083$).
  - The incidence of severe adverse events was similar in the two groups.

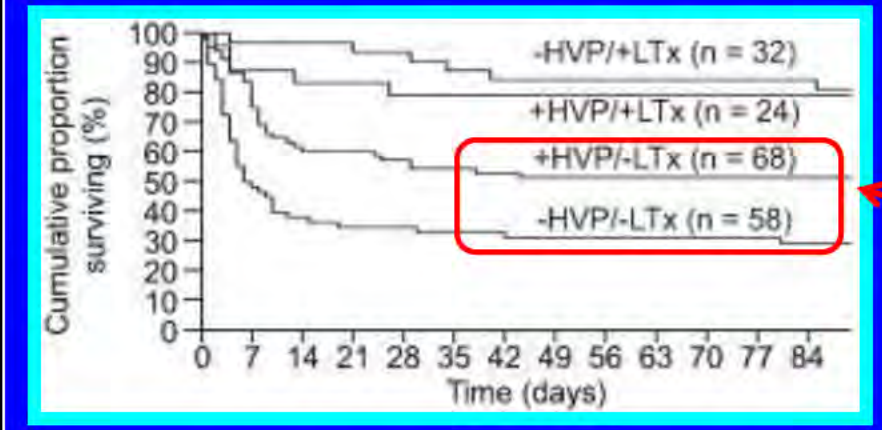
High-volume plasma exchange (HVPE) in patients with acute liver failure:

An open randomized controlled trial

Larsen FS et al. Journal of Hepatology, 2016-01-01, Volume 64, Issue 1, Pages 69-78

- **HVP PROTOCOL:**
- The volume of HVP Exchanged was 15% of ideal body weight (representing 8–12 L per day per procedure);
- Patient plasma was removed at a rate of 1–2 L per hour with replacement with fresh frozen plasma in equivalent volume.
- **CONCLUSIONS:**
- **Treatment with HVPE improves outcome in patients with ALF by increasing liver transplant-free survival** (in non-transplanted).
- **Attributed to attenuated innate immune activation and ameliorated multi-organ dysfunction.**





If transplanted:
CI 0.37 to 3.98; $p = 0.75$

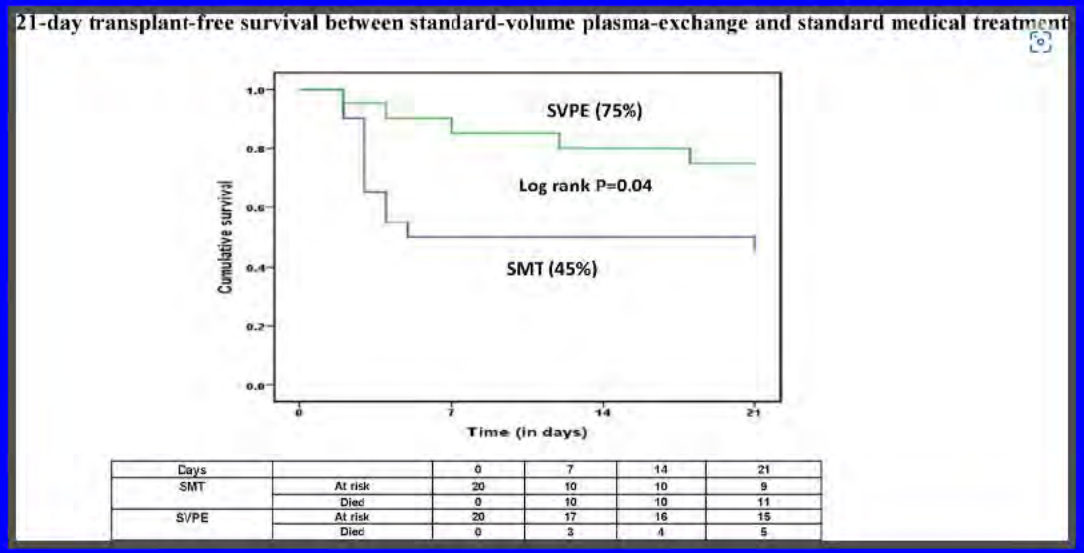
Only beneficial if not Transplanted

Standard-Volume Plasma Exchange Improves Outcomes in Patients With Acute Liver Failure: A Randomized Controlled Trial

Clinical Gastroenterology and Hepatology, 2022-04-01, Volume 20, Issue 4, Pages e831-e854

- 40 consecutive patients of ALF were randomized 1:1 to either standard medical treatment (SMT) or SMT with standard-volume plasma-exchange (SVPE)
- **RESULTS**:
- Higher lactate clearance (p = .02),
- Amelioration of SIRS (P = .02),
- Reduction in ammonia levels (P = .02) and
- Reduction of SOFA scores [P = .001].
- Higher 21-day transplant free-survival [75% vs. 45%; P = .04, HR 0.30, 95%CI 0.01-0.88]

SVPE [mean sessions 2.15 ± 1.42, median plasma volume replaced 5.049 L] compared to SMT alone



Target exchange volume of 1.5–2.0 plasma volumes per session. Replacement fluid used was 90% fresh frozen plasma and 10% normal saline

Minimize Risk of Brain Edema and Intracranial Hypertension

Early Recognition and Treatment of Hepatic Encephalopathy (Porto-Systemic Encephalopathy - PSE)

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Hepatic Encephalopathy (PSE)

- Defines FHF.
  - Increases risk of brain edema, intracranial hypertension, and infection
- Caution: exclude other causes of altered mental status
  - sedatives, - encephalitis, or - meningitis
- Causative Factors:
  - ammonia, - mercaptans, - glutamate,
  - benzodiazepine-like substances, - aromatic aminoacids.
- Progression can be rapid:
  - Neurologic-check every hour,
  - Avoid sedatives/sedating anti-emetics.

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Hepatic Encephalopathy (PSE)

Predictors of Severe PSE (III or IV): (Hepatology 2007;46:1844-1852)

- Arterial ammonia > 100 mcM/L (Normal: < 54 mcM/L)
- MELD > 32
  - All these patients should be treated for PSE

Concerns in PSE Grades III & IV:

- frequently associated with brain edema
- may cause sub-clinical seizures
  - EEG monitoring
- causes high risk for aspiration pneumonia.

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Treatment of Hyperammonemia

Crit Care Med 2020; 48:218–224
Crit Care Resusc 2020; 22:158–165.

- *Continuous renal replacement therapy (RRT) within 4 hour after ICU admission is effective in lowering circulating ammonia concentration, maintaining metabolic and thermal stability*
- *Early RRT use is associated with improved survival in ALF and is now a cornerstone for supportive care in patients with established or evolving hepatic encephalopathy*

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Treatment of Hyperammonemia

Crit Care Med 2020; 48:218–224
Crit Care Resusc 2020; 22:158–165.

CVVHDF started in < 4 h with median effluent rates of 43 (37-61) mL/kg/hr.

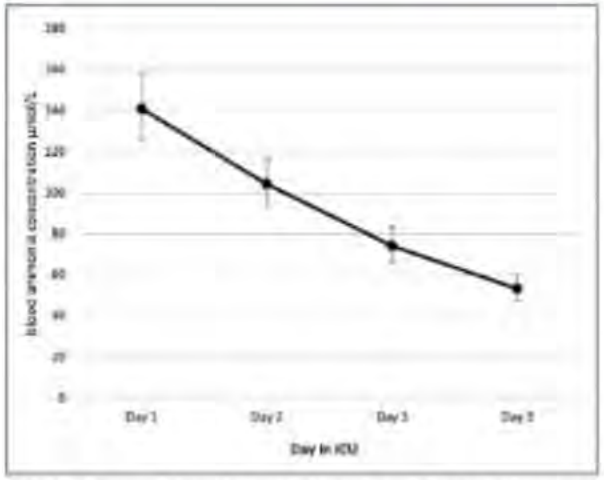

Figure 1. Ammonia dynamics over 5 d of treatment with continuous renal replacement therapy in acute liver failure. $p < 0.0001$. Geometric means of log transformed data. *Error bars* indicate 95% CI.

Ammonia Dynamics with CVVHDF

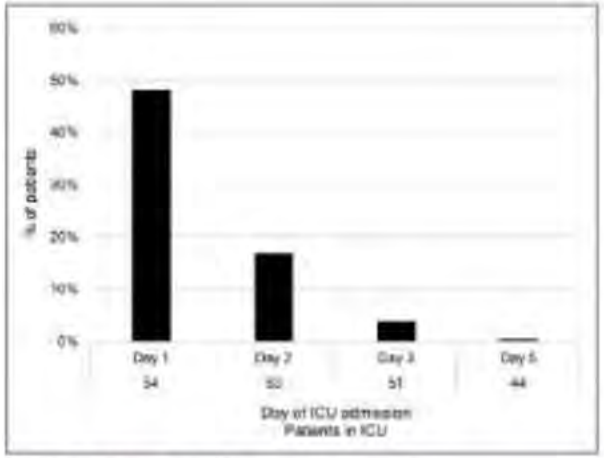

Figure 2. Proportion of patients with measured extreme hyperammonemia (> 150 μmol/l) over 5 d in ICU.

Proportion of Patients with Ammonia > 150 micromole/L

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Pharmacologic Management of Hepatic Encephalopathy

Lactulose:

- Increases intestinal elimination of ammonia
- Abdominal distention may make difficult to close abdomen after transplantation; discontinue after transplant listing.

Rifaximin:

- Decreases bacterial production of ammonia in the intestine

"Hepatic-BCAA enriched" tube-feed formula:

- Decreases formation of aromatic amino acids.
- Removed from the market.

L-carnitine;

- Decreases brain ammonia uptake;
- May increase seizure risk; consider D/C in PSE III-IV

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Management of Hepatic Encephalopathy

Airway Protection & Sedation

Crit Care Med 2007; 35:2498-2508

- In HE grade III or IV: intubate, sedate & ventilate;
  - Intubate: minimizing trauma (expert operator)
    - Cleanse mouth with chlorhexidine BID
  - Sedate: Propofol sedation not to exceed 80 mcg/kg/min (5 mg/kg/h)
    - in order to decrease risk of "Propofol infusion syndrome (PRIS)": acute refractory bradycardia leading to asystole, in the presence of one or more of the following:
      - metabolic acidosis (base deficit > 10 mmol/L),
      - rhabdomyolysis,
      - hyperlipidemia, and
      - enlarged or fatty liver .

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Hepatic Encephalopathy

Ventilation

Crit Care Med 2007; 35:2498-2508

- **Ventilate** to keep:
  - **Tidal Volume**: </= 6 mL/kg of "predicted or ideal body weight" in Kg (maximun 8 mL/kg)
    - http://www.ardsnet.org/node/77460
    - Males: PBW (kg) = 50 + 2.3 (height (in) – 60);
    - Females: PBW (kg) = 45.5 + 2.3 (height (in) – 60)
  - **Plateau Pressure**: < 30 cm H_2O
    - (high "peak" increases ARDS risk)
  - **Respiratory Rate**: to keep PCO_2 34-40 mmHg;
  - **PEEP**: Avoid/minimize PEEP (</= 12)
    - (high PEEP increases Intra cranial Pressure).

Early Recognition of Brain Edema and Intracranial Hypertension

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Cerebral Edema Risk & Repercussions

- Brain Edema Risk:
  - HE grade IV: 65-80% have cerebral edema;
  - HE grade III: 25-35% have brain edema.
  - Arterial ammonia > 200 mcg/dl is associated to severe brain edema with herniation
- Repercussions of Brain Edema:
  - Permanent brain damage due the length of extreme severity (>/= 2 hours):
    - Intra Cranial Hypertension (ICP > 25 mm Hg; extreme if > 50 mm Hg)
    - Decreased Cerebral Perfusion (CPP < 50 mm Hg; extreme if < 40 mm Hg)

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Cerebral Edema & Intra-cranial Hypertension

- **Intracranial HTN = ICP > 25 mmHg.**
  - Is the main or the second cause of death.
  - May be silent or give:
    - ***Cushing Reflex: arterial hypertension + bradycardia + irregular respiration***
    - Pupillary abnormalities: asymmetry, or dilation with sluggish response to light,
    - Decerebrate posturing, or epileptiform activity, or hypertonicity
  - Poor Dx tools: CT scan, fundoscopy, trans-cranial doppler, PET scan & MRI are not sensitive for IC HTN
  - **Best Dx Tool: Epidural intra-cranial transducer**
    - complication rate: epidural catheters (4%), subdural (20%), & parenchymal/intraventricular catheters (22%)

Management of Brain Edema Complications

Brain Edema

Management Parameters

Clinics in Chest Medicine, 2009-03-01, Volume 30, Issue 1, Pages 71-87

- Guided by **Cerebral Perfusion Pressure (CPP)** in mmHg = Mean Arterial Pressure (MAP) – Intra-Cranial Pressure (ICP)
- **Goal:** keep
  - **CPP : 60** mmHg to 80 mm Hg (best > 70) and
  - **ICP <** 25 mmHg (best < 20 mm Hg)
- Clinical use:
  - CPP < 40 x 2 hours contraindicates Liver Tx
  - ICP > 50 x 2 h = poor neurological recovery

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Intra-cranial Hypertension Management Options

- Decrease Brain Edema:
  - Induce hypernatremia:
    - Hypertonic saline, or
    - Osmotic diuretics (mannitol).
- Prevent brain accumulation of osmolar-active substances (ammonia, glutamate, etc):
  - CVVHDF started at ICU admission with median effluent rates of 43 (37-61) mL/kg/hr
  - Treat hepatic encephalopathy.
- Improve cerebral blood out-flow:
  - Head elevation of 30^0 (no if CPP < 50 mm Hg)
- Decrease Excessive Blood Flow without impairing cerebral perfusion:
  - Hypothermia (32-33 ^{0}C),
  - Barbiturate coma,
  - Indomethacin

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Intra-cranial Hypertension Management

- Avoid brain overhydration;
  - Keep serum Na 145-**150**:
  - Water restriction and maintain IV fluid with D10-Normal Saline
  - Correct intravascular volume with 0.9% NaCl, D5W 0.45% NaCl+75 mMo/L Na Bicarbonate (if acidotic or with hyperchloremia), or 5% albumin
  - Hypertonic saline (3%) when needed.
- Keep head **30^0** elevated (unless CPP < 50 mmHg)
- Propofol sedation;
- Avoid sudden head movement;
- Treat Hepatic Encephalopathy:

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Intra-cranial Hypertension Management

- Quiet room; do only indispensable interventions
- Endotracheal lidocaine for suction.
- Avoid “positive end-expiratory pressure” (PEEP)
- Avoid fever; keep temperature of 36.5 ^{0}C (97.7 ^{0}F)
- Treat arterial hypertension only if CPP > 110 mmHg & ICP > 20 mmHg.
  - Aggressive treatment of hypertension may decrease cerebral perfusion.

Risks of Inducing Hypernatremia

In severe hyponatremia, the frequency of demyelinating lesions due to correction of plasma sodium concentration is:

- Common if is raised more than 20 meq/L per day.
- Rare at a rate below 10 to 12 meq/L per day.

Late neurologic deterioration is rare if chronic hyponatremia is corrected at an average rate equal to or less than 0.5 meq/L per hour (12 mEq/L/day)

To be safe is better to raise serum Na by only 8 mEq/L/day (0.33 mEq/L/h)

FHF
Intra-cranial Hypertension Management
Crit Care Med 2007; 35:2498-2508;
Semin Liver Dis 2008; 28:188-200

Hypertonic 3% NaCl:

- **Volume in mL to be given over 24 h** = "Lean Body Weight (in Kg)" x "desired increase in Na (mEq/L)" (increase must be </= 8 mEq/L/day)
- **Lean Body Weight** formula (in Kg)
  - http://www.medcalc.com/body.html
  - LBW men= (1.10 x Weight(kg)) - 128($Weight^2/(100 \times Height(m))^2$)
  - LBW women = (1.07 x Weight(kg)) - 148($Weight^2/(100 \times Height(m))^2$)

Mannitol 20%

- **Initial dose:** 0.5 g/kg over 30 min if urine output > 30ml/h or while in CVVHF/SLED;
- **Goal:** Keep Osm > 310 & < 320;
- **Monitoring:** serum Osm q 4h
- **Re-dosing:** mannitol 0.5 g/kg when Osm < 305.
- **CVVHF/SLED management:** remove 3-5X volume of mannitol given.

FHF
Intra-cranial Hypertension
Management
Crit Care Med 2007; 35:2498-2508
Semin Liver Dis 2008; 28:188-200

Hypothermia (decreases cerebral blood flow)

- **Candidates:** Hypernatremia non-responders (mannitol or 3% NaCl).
- **Goal:** Core temperature of 32-33 ^{0}C for up to 5 days. Slow rewarming of 1 ^{0}C per each 12 hours; try to rewarm every 24 h, and re-cool if ICP raises.
- **Monitoring:** ICP, CPP.
  - Needs sedation & analgesia.
  - Cisatracurium is used for paralysis (shivering control).
  - Risk of infection and arrhythmia.

Thiopental (decreases cerebral blood flow)

- **Candidates:** Hypernatremia & Hypothermia contraindication/non-response.
- **Dose:** 5 mg/kg IV over 15 min and followed by 3-5 mg/kg/h to keep ICP and CCP under control.
- **Monitoring:** EEG (Neurologist), ICP, CPP.

FHF
Intra-cranial Hypertension Management

Continuous EEG Monitoring vs	Daily + Event guided EEG	Prophylactic Levetiracetam (Keppra) or Phenytoin is NOT Recommended but has been used in:
	• Treat Seizure activity with Levetiracetam or Lacosamide, or Phenytoin +/- Versed	• Grade III or IV Hepatic encephalopathy. • Sudden neurologic deterioration. • Myoclonus

Avoid Hypoglycemia & other Complications

FHF Metabolic & other Complications

Hypoglycemia:

- Occurs in 45%.
- Check glucose q 2 h and keep > 110 mg/dL and < 180 mg/dL; Insulin if > 180-200
- Give D10, D20, or D50 (D10-NS to avoid overhydration)
- **Naso-jejunal TEN** > 60% of needs (double-lumen N-G-J tube) (Two-Cal or Hepatic-BCAA enriched formula)

Acute Pancreatitis: due to tissue hypoxemia.

Acid-base disorders: ABGs and lactic acid levels

Electrolyte disturbances:

- Follow BMP, phosphorus, Mg, Ca and correct abnormalities.
- Hyperphosphatemia is a marker of poor outcome.

Prophylaxis for hemorrhagic gastritis: PPI until in tube feeds.

ICU Management of ACLF and ALF

Nanchal R et al. Critical Care Medicine March 2020 • Volume 48 • Number 3; e173-191

- Target a serum blood glucose of 110–180 mg/dL in patients with ALF or ACLF.
- Use enteral nutrition over parenteral nutrition in critically ill patients hospitalized with ALF or ACLF without contraindication for enteral feeding.
- Target nutrition with protein goals comparable to critically ill patients without liver failure (1.2–2.0 g protein/kg dry or ideal body weight per day). BCAA formulas should not be used routinely.

Manage Hemodynamic Compromise

FHF

Hemodynamic Management

Crit Care Med 2007; 35:2498-2508
Semin Liver Dis 2008; 28:188-200;
Hepatology 2012; 55:965-967
Nanchal R et al. Critical Care Medicine March 2020 • Volume 48 • Number 3; e173-191

- **Hypotension** occurs in 20% of FHF patients. It is defined as:
  - BPs < 85 or MAP < 60 in normotensive, or
  - MAP </= 80 mmHg in patients who suffer from hypertension.
- Initial Basic Management:
  - Resuscitate with **colloids** (5% albumin) & crystalloids (0.9% NaCl or 0.45% NaCl + 75 mMol/L Na bicarbonate)
  - Keep CVP 8-10 cmH_2O or adequate IVC filling by bedside serial ECHO (but lack of data)
  - **AVOID BOTH VOLUME OVERLOAD and VOLUME DEPLETION**
  - Keep serum Na high normal (145-150)
  - MAP goal is >/= 65 mm Hg (if not previously hypertensive)

FHF

Hemodynamic Management

- **N-acetyl-cysteine**: improves O_2 delivery and decreases lactate production.
  - **Oral: 140 mg/kg loading and 70 mg/kg q 4 hours p.o., or**
  - **IV** (maximally concentrated in 0.45% NaCl): **day 1: 150 mg/kg IV over 1 hour, then 50 mg/kg over 4h; then 100 mg/kg over 16 h; days 2-5: 150mg/kg/d until INR < 2**

FHF Hemodynamic Management

- **Alfa-agonists, & vasopressin as needed**
  - **Alfa-agonists:** Norepinephrine (0.01-**0.1**-3 mcg/kg/min) +/- Phenylephrine (0.4-1.4-9.1 mcg/kg/min) +/- Vasopressin (0.6-1-4 IU/hour) once Norepinephrine is > 0.3 mcg/kg/min, or Terlipressin for "volume unresponsive" hypotension, if
    - MAP < 60 mmHg in "previously normotensive" **(goal > 65)**
    - MAP < 80 mmHg in "previously hypertensive" **(goal = 85)**
  - **Vasopressin/Terlipressin is NOT contraindicated in ALF (Eefsen** M et al. J Hepatol 2007;47:381-386) (Hepatology 2012; 55:965-967) (Journal of Hepatology 2017 vol. 66 j 1047–1081)
    - Vasopressin 0.6-1-4 IU/h (usually 1-2 U/h, once norepinephrine > 0.3 mcg/kg/min)
- **Inotropics:**
  - Dopamine >/= 5 – 130 mcg/kg/min **added** if
    - not responding to "volume" + alfa-agonists + vasopressin, or
    - $ScvO_2$ or SvO_2 < 70% with Hct >/= 30, or
    - cardiac index < 3.5 L/min/m^2 + low perfusion

Starting dose in white number

FHF Hemodynamic Management

- **Evaluate for adrenal insufficiency and/or treat**
  - Obtain "basal Cortisol" and give Cortrosyn 250 mcg bolus intravenously; then:
  - 30 minutes and 60 minutes after the Cortrosyn, obtain blood samples for "post stimulation" serum cortisol (and "free-cortisol" if albumin is </= 2.5 g/dL).
  - If all 3 cortisol samples are </= 30 mcg/dL or if the post Cortrosyn increase-response is < 9 mcg/dL: Treat with Hydrocortisone IV 100 mg every 8 hours.
  - Once "free cortisol" samples are back, reassess if treatment was for a "false positive" and if hydrocortisone should be discontinued.
- **Hepatectomy**

Protect Renal Function

FHF

Renal Failure Management

- Renal failure occurs in 40-85% of FHF.
- Prevention, Evaluation & Management:
  - Avoid aminoglycosides, NSAID's, IV contrast.
  - Correct volume depletion and hypotension; Avoid volume overload
  - Protect kidney with NAC.
  - Obtain urine analysis + microscopic exam + Eos; Ultrasound of kidneys for renal dz/obstruction.
  - In ATN, consider early bicarbonate –buffered SLED/CVVHF.
  - Once in SLED/CVVHF goal MAP of 60 mm Hg is enough.

FHF
Renal Failure Management

Hepatorenal syndrome (HRS):

- AKI (creatinine increase > 0.3 non-responsive to volume), or Low GFR (Cr > 1.5 mg/dL or CrCl < 40 ml/min)
- Absence of: shock, nephrotoxin, volume depletion.
- No Response to: diuretic withdrawal + 1g/kg 5% albumin infusion.
- Proteinuria < 500 mg/dL &
- U/S without obstruction or parenchymal renal disease.

In HRS after normalization of CVP with albumin & NS:

- Midodrine 7.5-20 mg po TID + Octreotide 100-200 mcg SQ TID + albumin for CVP 8-10, to keep MAP =/> 85 mmHg or
- **Norepinephrine to increase MAP to 85 mmHg + albumin for CVP 8-10**

Consider Misoprostol

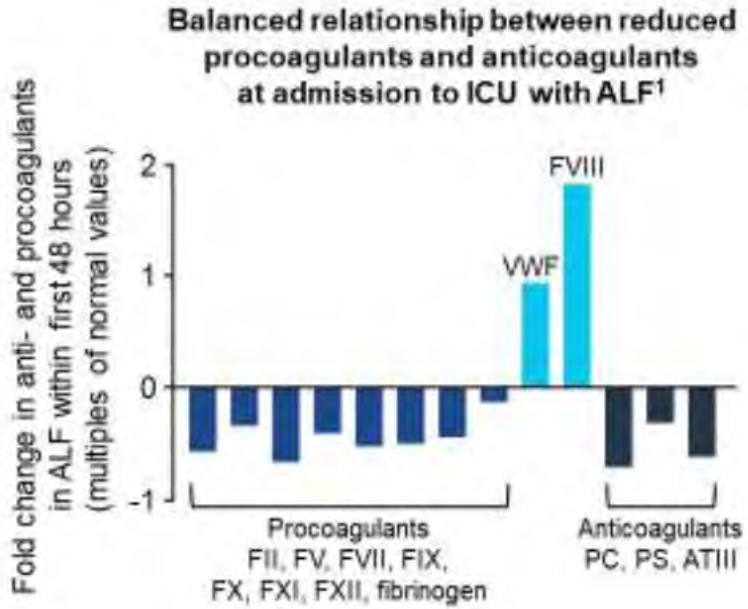
Minimize Risk of Bleeding

FHF
Coagulopathy/Bleeding

Prolongation of PT (after Vitamin K replacement) is a reliable indicator of prognosis and evolution;	Factor V activity has prognostic value (see later).	Prophylactic platelets: only if
• repeat daily (not useful if in High volume plasma exchange).		• =/< 10,000, or • =/< 20,000 with petechiae or mucosal bleed. • **Dose:** 1 unit per 10 kilograms of body weight when using random pooled platelets, or one unit of single donor platelets per transfusion episode will increase plat by 5,000 to 10,000

Coagulation: monitoring and management

- Rapid changes in PT or INR are characteristic of ALF
  - Significant prognostic value
- Common in ALF
  - Thrombocytopenia
  - Reduced circulating pro- and anti-coagulant proteins
  - Increased PAI-1
- Abnormal coagulation does not translate to increased risk of bleeding
  - Most patients' coagulation is normal despite abnormal INR and PT



1. Agarwal B, et al. J Hepatol 2012;57:780–6;
EASL CPG ALF. J Hepatol 2017;66:1047–81

PAI-1: Plasminogen Activator Inhibitor type 1

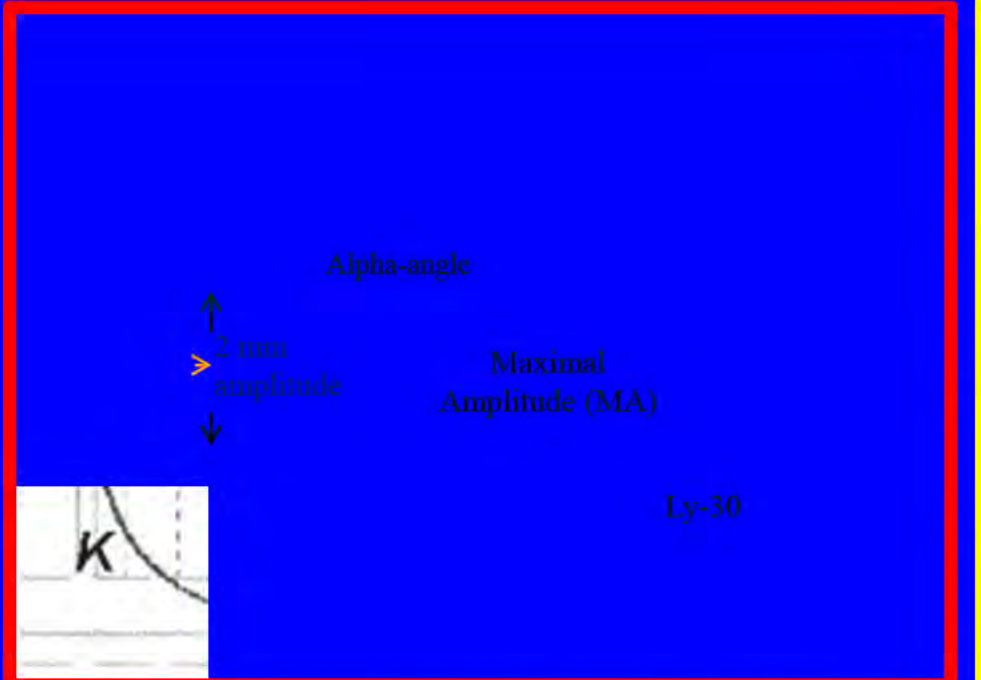
FHF

Coagulopathy/Bleeding

- Correct coagulopathy for invasive procedure or bleeding:
  - Platelets < 50K:
    - a) Random pooled platelets: 1 unit per each 10 kilograms of body weight, or
    - b) Single-donor apheresis platelets
      - Platelet transfusion is more effective in improving thromboelastogram (and coagulation) than fibrinogen (cryoprecipitate) transfusion.
  - Fibrinogen < 100 mg/dL, or < 150 mg/dL with bleed:
    - One "pre-pooled unit" (that contains 5 cryoprecipitate units for a total volume of 90 to 100 mL) of cryoprecipitate per 70 kg of weight, increase fibrinogen by 35 mg/dL; goal is Fibrinogen >/= 120 mg/dL (but > 150 mg/dL if bleeding occurs).

Interpretation of Thromboelastogram

Modified from Journal of Hepatology 2012 vol. 56 j 129–136

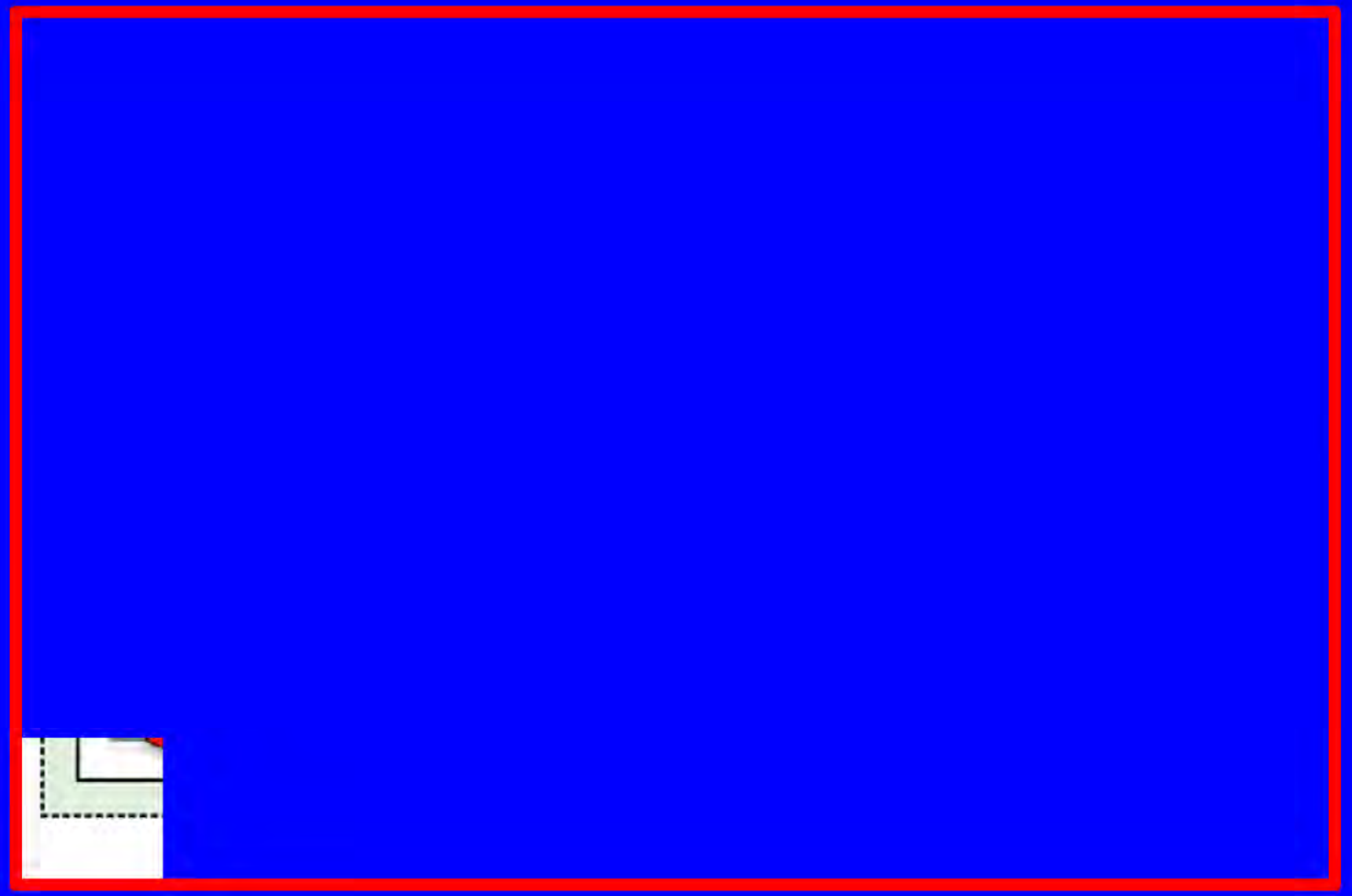


Hypocoagulation: High R-time, High K-time, Low alpha angle, Low MA

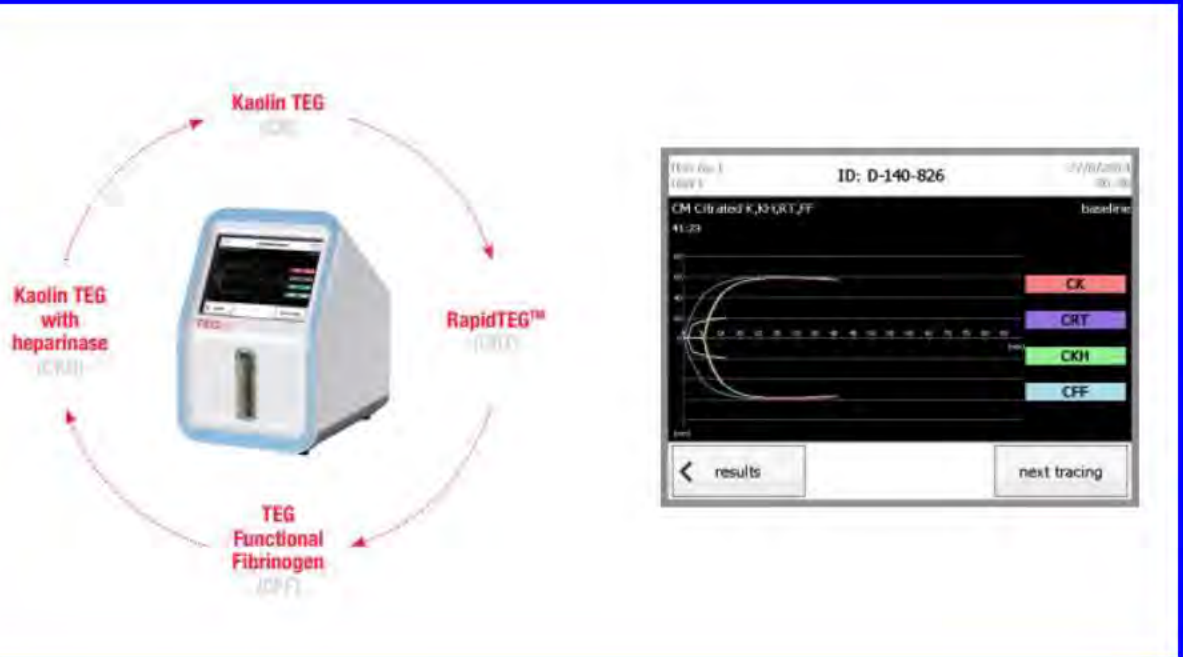
Hypercoagulation: Low R-time, Low K-time, High alpha angle, High MA

- **R-time** (in minutes): the latency of clot formation from the beginning of the clotting reaction to the initial formation of fibrin (defined as an amplitude of 2 mm). N= 4.6-9.1 (high = hypo-coagulation & worse prognosis)
- **K-time** (in minutes): the time from initial fibrin formation required to reach a specific clot firmness (defined as an amplitude of 20 mm). N = 0.8-2.1 (high = hypo-coagulation)
- **alpha-Angle** (in degrees): the kinetics of clot formation, measuring the rate of fibrin formation and cross-linking on platelets. N = 63-78 (low = hypo-coagulation)
- **MA** (in mm): measures the maximal clot strength. N = 52-69 (low = hypo-coagulation)
- **Lysis at 30 min** (Lysis-30; in percent): clot dissolution 30 min after reaching maximum amplitude, a measure of fibrinolysis. N = 1-7.5
- **Interpretation:** An abnormal TEG parameter with hypo-coagulation is defined as an R- or K-time above the upper limit of normal, or an a-angle or MA below the lower limit of normal

Thromboelastography guiding Prophylactic Management of Coagulopathy



TEG 6s



Test	Description	Clinical Value
Kaolin TEG (CK)	An intrinsic activated assay.	Identifies underlying hemostatic characteristics and risk of bleeding and thrombosis.
Rapid TEG (CRT)	An intrinsic and extrinsic pathway activated assay.	More rapidly assesses patient hemostasis properties.
Kaolin TEG with Heparinase (CKH)	Eliminates the effect of Heparin in the Test Sample	Used in conjunction with Kaolin TEG, assesses the presence of systemic heparin or heparinoids.
TEG Functional Fibrinogen (CFF)	Extrinsic Pathway Activated Assay uses a potent GP IIb/IIIa platelet inhibitor to restrict platelet activity	Isolates fibrin contribution to clot strength and, used in conjunction with Kaolin TEG, assesses relative contribution of platelets and fibrinogen to overall clot strength.

UofL TEG-6s Guided Management of Abnormal Coagulation in Liver Disease

Cirrhosis or Acute Liver Failure with Bleeding, or Before Moderate or Severe Bleeding-Risk Procedure

Modified from: Gish RG et al. Gastroenterology & Hepatology Volume 17, Issue 1, Supplement 1 January 2021

Measure Fibrinogen level, Platelet count, TEG-6s and look for "bleeding in puncture sites". Consider Factor VIII level.

K-Fibrin Time & Angle (K 0.8-2.1 min reference range) (Angle 63-78 degrees reference range)

- If R and MA are normal and K-time and Angle are abnormal: consider cryoprecipitate
- K > 2.1 min: consider 1-2 pre-pooled Units Cryoprecipitate.
- Angle < 63 degrees: consider 1-2 pre-pooled Units' cryoprecipitate.
- *Recheck TEG if cryoprecipitate has been given and patient is not improving, consider platelets*

Bleeding in Puncture Site:

a) Correct Fibrinogen to >/= 150 and Platelets to > 50K.

b) If bleeding persist, give Tranexamic Acid 1 gm IV q 6h until bleeding controlled.

Factor VIII measurement: Low level supports DIC; High level supports Localized Cirrhotic Fibrinolysis.

R–Latency Coagulation Time (4.6-9.1 min reference range)

- < 4.6 min hypercoagulable
- 9.2-12 min: give 1u FFP
- 13-15 min: give 2u FFP
- >15 min: give 3u FFP

GIVE FFP IN ALF WITHOUT PLANNED PROCEDURE, ONLY WHEN INR > 7, TO KEEP INR BETWEEN 5-7

Low Fibrinogen < 150 mg/dL:

Give cryoprecipitate to reach >/= 150 mg/dL.

Each pooled cryoprecipitate unit (5 units) will increase Fibrinogen by 25-50 mg/dL in a 70 kg person.

MA–Prior to Invasive Procedure

- If platelet count is <20,000 and MA <52: consider TPO agents if time to plan the procedure, or 2 U Single Donor Platelets (SDP).
- If platelet count is between 20,000 and 60,000 and MA is <52 and a procedure is planned, use TPO agonist to avoid platelet transfusions if time to plan the procedure, or 1 U Single Donor Platelets.

MA–Platelet Function (52-69 reference range bleeding)

- 48-51 mm: Consider 0.3 mcg/kg DDAVP, in the presence of uremia, or 1 Unit Single Donor Platelets if not uremic.
- ≤ 47 mm: Consider 1 Unit Single Donor Platelets.

1 pre-pooled cryoprecipitate unit = 5 cryoprecipitate units = 1389 mg Fibrinogen in a volume of 75-90 mL
Each pooled-unit should increase Fibrinogen by 25-50 mg/dL in a 70 kg person

Treat Infections Early

FHF

Infection

Predisposing Factors:

- Low opsonins & complement,
- Gut-bacteria translocation,
- WBC dysfunction,
- Lines & catheters,
- Immunosuppressive cytokines, …

Bacterial infection in 60-80%;

- Gram(+) in 80%: mostly Staphylococcus.
- Gram(-) in 20%: E.coli, Pseudomonas, Klebsiella
- Pneumonia 50%, bacteremia 26%, UTI 22%.

Fungemia in 30%;

- Usually late and with bacteremia.
- Poor prognosis.

FHF

Infection

Early Diagnosis:

- Daily blood, sputum, urine & line cultures.
- Daily fungal cultures

Risk Minimization:

- Remove intrauterine devices (IUDs), body piercing, unnecessary lines/catheters.
- TEN to decrease gut-bacteria translocation

Early Intervention:

- Neutropenia: filgrastim (Neupogen), or GM-CSF
- Guided broad-spectrum antibiotics and anti-fungals by 1 of 3 criteria (see later)

Bacterial, or Fungal Infection contraindicates Liver Transplant.

FHF

Infection

- Empiric broad spectrum antibiotic and antifungal for:
  - Rapid progression to stage IV encephalopathy.
  - Refractory hypotension,
  - SIRS by two of the following
    - 1) Temperature > 38ºC or < 35ºC,
    - 2) Heart rate > 90 beats/min,
    - 3) Respiratory rate > 20 breaths/min or PaCO2 < 32 mmHg ,
    - 4) WBC > 12,000 cells/mm3, < 4000 cells/mm3, or > 10 percent immature (band) forms.

FHF

Specific Therapies

- **Acute Fatty Liver of Pregnancy**: Delivery
- **Acetaminophen**:
  - Activated charcoal 1 gm/kg + N-acetyl-cysteine,
  - Molecular Absorbent Recirculating System (MARS)
  - Fomepizole 15 mg/kg IV single dose (if acetaminophen (µg/mL) and ALT (IU/L)) drawn at the same time are multiplied together and yield a value of >10,000 µg/mL * IU/L; Wong A et al. Clinical Toxicology. 2015;53(8):807-14). Only case series studies.
- **Mushroom (Amanita)** :
  - Activated Charcoal to decrease toxin absorption
  - PNC 7 million q 4 hour IV (toxin binding?),
  - Silibinin 30-40 mg/kg/day x 4 days (milk thistle is 70% sylimarin)
  - Silymarin 300 mg BID PO or by NGT
  - Legalon-SIL: 5 mg/kg/day IV (given in 4 divided doses) or 5 mg/kg IV loading dose followed by 20 mg/kg/day via continuous infusion. Blocks hepatocyte uptake of amatoxin. (request toll free # 866-520-4412, or Ketty Belizaire 908-566-8260, or Todd Mitchell MD 831-227-6048). Given x 3-4 days.
- **Autoimmune hepatitis**: 40-60 mg/d Prednisone +/- Imuran

Fomepizole Mechanism of Action

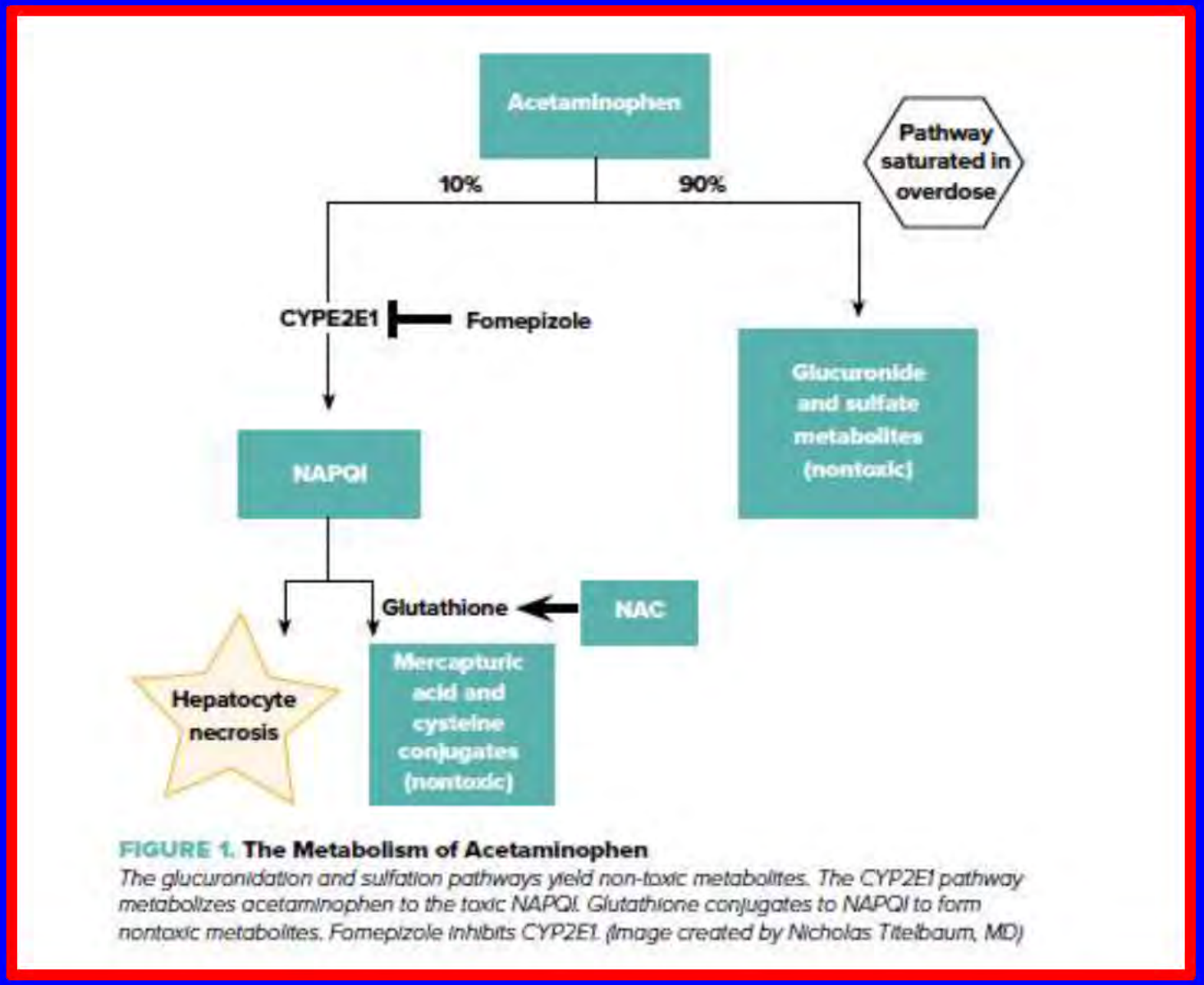


FIGURE 1. The Metabolism of Acetaminophen

The glucuronidation and sulfation pathways yield non-toxic metabolites. The CYP2E1 pathway metabolizes acetaminophen to the toxic NAPQI. Glutathione conjugates to NAPQI to form nontoxic metabolites. Fomepizole inhibits CYP2E1. (Image created by Nicholas Titelbaum, MD)

FHF

Specific Therapies

- **Wilson's**:
  - Zn 50-60 mg TID to decrease hemolysis;
  - NAC;
  - MARS or continuous hemofiltration;
  - Liver Transplantation.
- **HSV or EBV or VZ**: Acyclovir 10 mg/kg (by IBW) IV q 8h adjusted by kidney function.
- CMV: Ganciclovir 5 mg/kg IV every 12 hours (using IBW) adjusted for kidney function.
- **Chronic HBV re-activation with ALF presentation** (anti-HBcIgM s/n ratio < 5.08 in 79%, & HBV-DNA in millions IU/mL):
  - Tenofovir improves survival
    - in acute HBV with ALF, therapy may worsen outcome

Liver Transplant in Fulminant Hepatic Failure

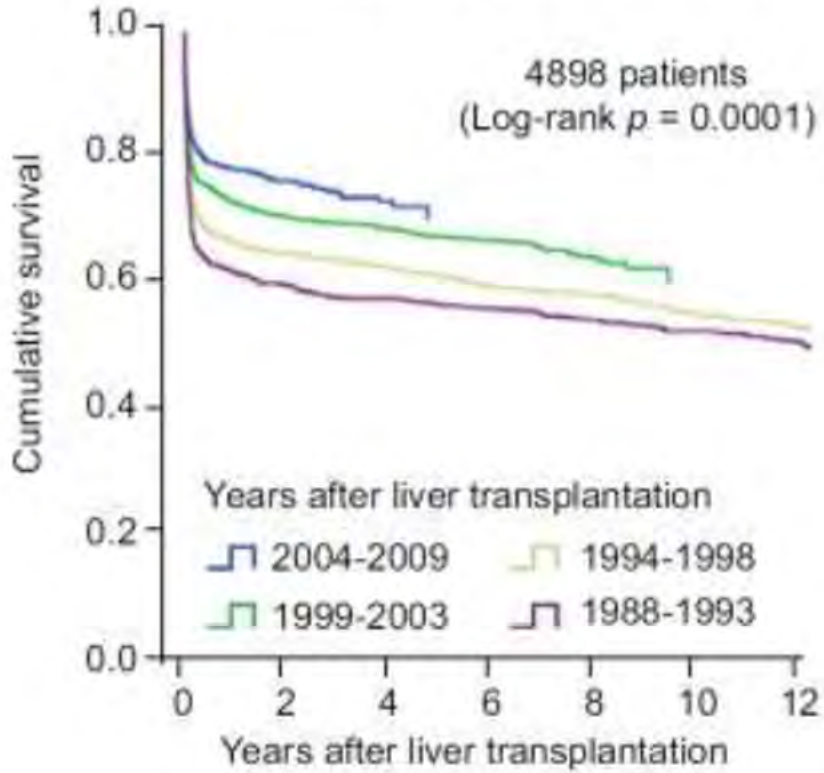
Liver Transplant in Fulminant Hepatic Failure

- **Mean waiting time = 3.3 days (2000-2003)**
- **Receive ABO incompatible liver = 11%** (1.9% in chronic ESLD)
- **Patient survival: 1 year = 91% in ALFSG** (78-85% in chronic ESLD).
- **Graft survival: 1 year = 75% (2000-2003)** (70% in chronic ESLD)

Impact of liver transplantation in ALF

- LTx has been the most significant development in the treatment of ALF in 40 years and has transformed survival
- 1-year survival following emergency LTx for ALF is now around 80%
- Selection for LTx depends on:
  - Accurate prediction of survival without transplant
  - Consideration of the survival potential after LTx
  - Consideration of whether a patient is too sick to transplant

Patient survival after liver transplantation for ALF, Europe 1988–2009[1]

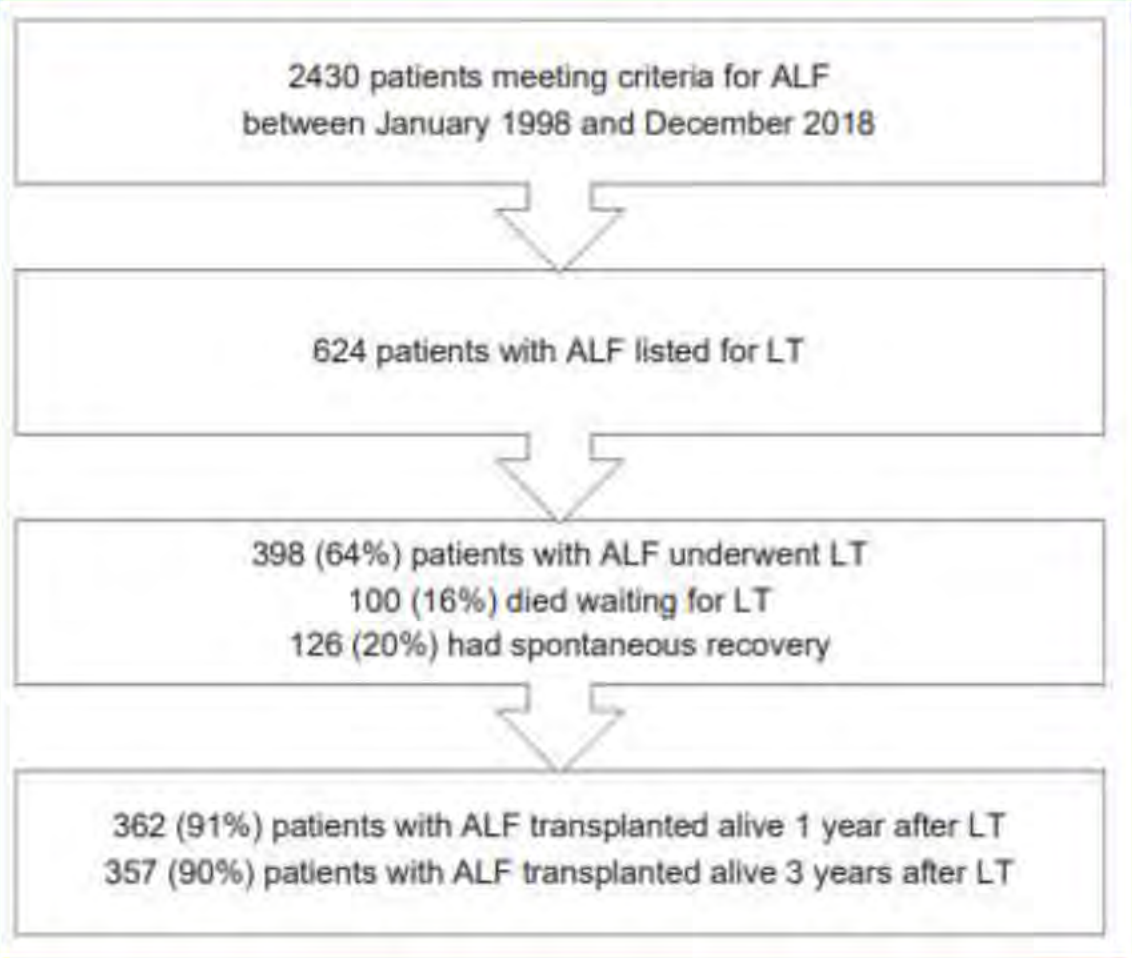


p<0.001 for survival 2004–2009 vs. previous time periods

1 Germani G, et al. J Hepatol 2012;57:288–96; EASL CPG ALF. J Hepatol 2017;66:1047–81

Outcomes of patients with acute liver failure listed for liver transplantation

Karvellas CJ et al. Liver Transplantation. 2022;00:1–13.



Requirements for 1A listing

- Fulminant liver failure, defined as the onset of hepatic encephalopathy within 56 days of the first signs or symptoms of liver disease. Patient must be in ICU and have at least one feature (INR >2, be ventilator dependent, or require dialysis (CVVH or CVVHD)).
- Primary non-function of a transplanted whole liver within 7 days of transplant, with aspartate aminotransferase (AST) greater than or equal to 3,000 U/L and at least one feature (INR>2.5, Arterial pH</=7.3, Venous pH<7.25, Lactate >/=4)
- Primary non-function within 7-days of transplant of a transplanted liver segment from a deceased or living donor, evidenced by at least one feature (INR>2.5, Arterial pH</=7.3, Venous pH<7.25, Lactate >/=4).
- Hepatic artery thrombosis (HAT) within 7-days of transplant, with AST greater than or equal to 3,000 U/L and at least one feature (INR>2.5, Art pH</=7.3, Venous pH<7.25, Lactate >/=4).
- Acute decompensated Wilson's disease.
- Anhepatic

Predictors of Outcome

Predictor of Good Outcome Without Transplantation

A 3-fold increase of AFP from day 1 to 3,
or
AFP > 3.9 mcg/L or ng/mL one day after peak ALT,

suggests survival without transplantation.

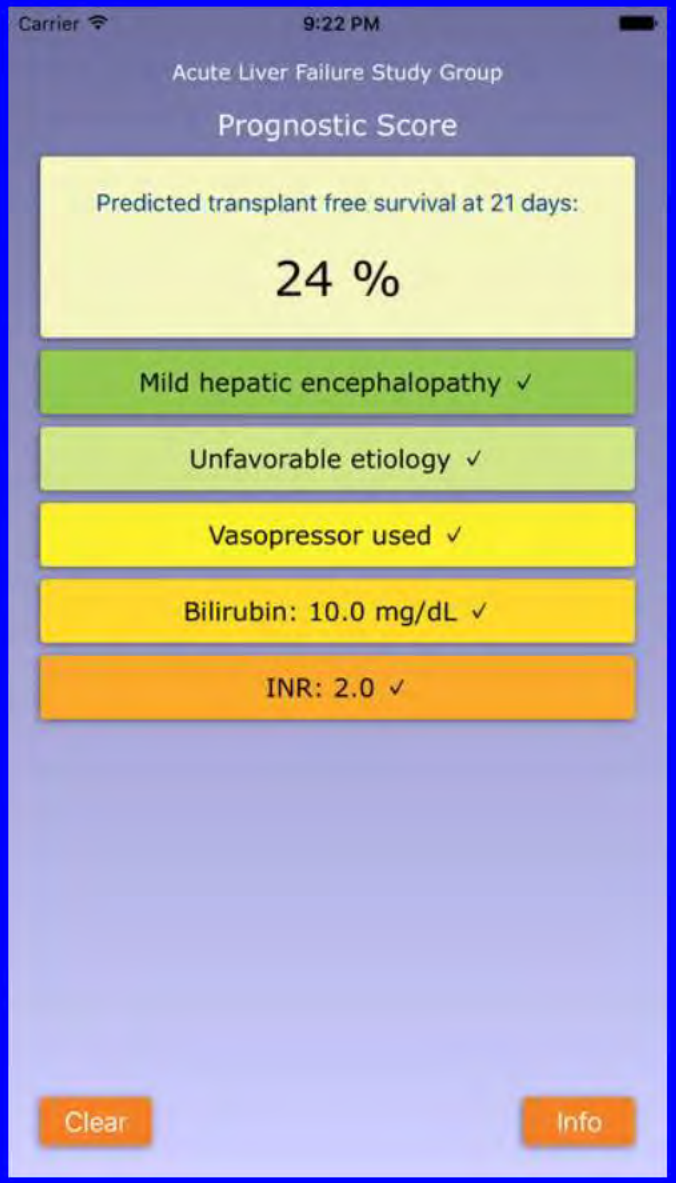
Predictors of Poor Outcome Without Transplantation

ALFSG Prognostic Score (ALF Prognostic)

- Predicts 21-day Spontaneous Survival in patients with ALF.
- Multivariable Logistic Regression:
  - Derived from 878 subjects enrolled into the ALFSG database from January 1, 1998 through June 11, 2013
  - Development cohort: 481 subjects
  - Validation cohort: 482 subjects

ALFSG Prognostic Score

- Logit SS = 2.67 - 0.95(HE*) + 1.56(Etiology*) - 1.25(Vasopressor Use*) - 0.70 (ln bilirubin) - 1.35 (ln INR).
  - For Mild (1-2) HE insert 0, for Deep (3-4) HE insert 1
  - For Unfavorable Etiology insert 0, for Favorable Etiology insert 1
  - For absence of vasopressor use insert 0, for vasopressor use insert 1.
-
- Predicted SS = $1/(1 + e^{(-1*\text{Logit SS})})$


Carrier
9:22 PM
Acute Liver Failure Study Group
Prognostic Score
Predicted transplant free survival at 21 days:
24 %
Mild hepatic encephalopathy ✓
Unfavorable etiology ✓
Vasopressor used ✓
Bilirubin: 10.0 mg/dL ✓
INR: 2.0 ✓
Clear
Info


ALF
Prognostic

Acute Liver Failure Early Dynamic (ALFED)

Kumar R et al. Gut 2012; 61: 1068-1075

ALFED Model (Score 1-6)

Variables over 3 days	Score assigned
Hepatic encephalopathy (persistent or progressed to grade >2)	2
INR (persistent or increased to >/= 5)	1
Arterial ammonia (persistent or increased to >/=123 micro-Mol/L	2
Serum bilirubin (persistent or increased to >/= 15 mg/dl)	1

- The Score stratify the risk of dying or surviving based in the evolution over 3 days (score 1 through 6) of hospitalization.
- Score of 1–3: survival frequency of about 80% or more.
- Score >/= 4: mortality risk of >80%.
- An ALFED score of >/= 4 had a high PPV (85%) and NPV (87%) for mortality
- Superior to KCC and MELD

MELD for Liver Transplantation

MELD Score > 30.5 predict need for transplantation.

Is used dynamically to assess evolution

The MELD score has been evaluated in 6 studies involving 526 ALF patients, of whom 58% died.

To predict mortality without Transplantation (MELD > 30.5):

- Sensitivity is 77% (range 70-92%) and
- Specificity is 72% (range, 56%–85%),
- Diagnostic odds ratio, 8.79; 95% CI, 5.19–14.89)

UK revised criteria for acute liver failure emergency liver transplant listing

Acetaminophen ALF	Non-Acetaminophen ALF
1. pH <7.25 more than 24 h after ingestion and after fluid resuscitation	Favorable causes (viral/ecstasy) with any grade HE and -INR > 6.5 (PT > 100 s), or -3 of: INR > 3.5 (PT > 50 s), age <10 or >40, bili > 3.4 mg/dl, Jaundice to Encephalopathy >7 days
2. All the following: INR >6.5 (PT > 100 s) Creatinine >3.4mg/dl HE grade 3	Unfavorable causes (indeterminate, DILI idiosyncratic) and -INR > 6.5 (PT > 100 s), or -In the absence of HE: INR > 3.5 and age <10 or >40 -In presence of HE: bilirubin >17.5mg/dl and J-E >7 days
3. Liver injury, coagulopathy and HE with: Arterial lactate >5 mmol/l on admission Arterial lactate >4 mmol/l >24 h after admission Exclusion of other causes of elevated lactate	Acute presentation of Wilson disease or Budd–Chiari syndrome with: -Combination of any grade of HE and coagulopathy
4. Two of three criteria from category 2, in the absence of sepsis, with other evidence of organ failure deterioration	

Wilson's Disease

- Modified Nazer's score for WD & OLTx
- Validated in children (Liver Transpl 2005;11:441-448) & adults (Liver Transpl 2007;13:55-61)
- **Score =/> 11, or INR =/> 7 needs OLTx**; all other can receive chelation therapy.

Points	Bili	AST	INR
0	<5.84	<100	<1.3
1	5.85-8.7	100-150	1.3-1.6
2	8.8-11.6	151-200	1.6-1.9
3	11.7-17.5	201-300	1.9-2.4
4	>17.5	>300	>2.4

Historical Prognostication Tools (no longer used)

FHF

Predictors of Poor Outcome Without Transplantation

Kings College Criteria (KCC)

Predictor of Mortality

- **Acetaminophen** (PPV= 0.95 NPV= 0.78)
  - Arterial pH < 7.3
  - PT with INR > 6.5 + creatinine > 3.4 mg/dL

FHF

Predictors of Poor Outcome Without Transplantation

Kings College Criteria (KCC)

Predictor of Mortality

- **Non-Acetaminophen** (PPV=1.0; NPV=0.3)
  - Patient with INR > 6.5, or
  - Three of the following:
    - Age < 10 or > 40
    - Drug reaction or FHF of indeterminate cause
    - Jaundice > 7 days before encephalopathy
    - PT with INR > 3.5
    - Bilirubin > 17.6 mg/dL

FHF

Predictors of Poor Outcome Without Transplantation

Clichy criteria

Predictor of Mortality

- **Acute Viral Hepatitis** (PPV=0.89, NPV=0.36)
  - Age < 30 & Factor V < 20 mg/dL, or
  - Age > 30 & Factor V < 30 mg/dL

If patient is Transplant candidate

Transfer to Transplant Center

Other Predictors of Poor Outcome without OLTx

Liver Bx	**Necrosis > 70%**
Arterial Ammonia	**> 150 uM**
Arterial Lactate	**> 3.5 mM (APAP)**
Arterial Phosphate	**> 1.2 mM (APAP)**
APACHE score at admission	**> 15 (APAP)**

Keeping Na 145-150 mEq/L

Volume of 3% NaCl Needed to raise Na by 8 mEq/L

- Sodium Deficit = Total Body Water x (desired Na - actual Na) 8
- TBW = lean body weight (kg) times 0.5 for women, or 0.6 for men.
- To raise Na by 8 mEq (desired Na– actual Na = 8), replace the
  - Na Deficit = [Lean body weight (kg) x 0.5] x 8 mEq = mEq to be given over 24h
- 3% NaCl (hypertonic saline) has 513 mEq/L of Na = 0.51 mEq/mL
- **Total volume of 3% NaCl (mL) to be given over 24 h =**
  - Na Deficit / 0.51 mEq/mL = [Lean body weight (kg) x 0.5 L/kg] x 8 mEq/L / 0.51 mEq/mL = mL

Keeping Na 145-150 mEq/L

Volume of 3% NaCl Needed to raise Na by 8 mEq/L

- Sodium Deficit = Total Body Water x (desired Na - actual Na)
- TBW = lean body weight (kg) times 0.5 for women, or 0.6 for men.
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- 3% NaCl (hypertonic saline) has 513 mEq/L of Na = 0.51 mEq/mL
- **Total volume of 3% NaCl (mL) to be given over 24 h =**
  - Na Deficit / 0.51 mEq/mL = [Lean body weight (kg) x 0.5 L/kg] x 8 mEq/L / 0.51 mEq/mL = **Lean Body Weight (in kg) x 8**

FHF
Expected Survival by Etiology

	%
• Wilson's dz	**0**
• Cryptogenic	**< 20**
• Idiosyncratic	**< 20**
• Halothane	**< 20**
• Hep A/B+brain edema+ARF	**30**
• Hep A/B+brain edema	**50**
• Hep A/B+ HE 3/4 (no brain edema)	**67**
• Tylenol+brain edema+ARF	**53**
• Tylenol+brain edema	**71**
• Tylenol+ HE 3/4 (no brain edema)	**100**