

Acute Liver Failure

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Learning Objectives

- Clinical Definition
- Epidemiology
- Etiologies/Etiology-Specific Management
- Diagnosis
- Prognosis
- Complications and Management
- Long Term Outcomes

Acute Liver Failure

Fulminant Hepatic Failure

- Most severe form of liver injury by rare
- Devastating: survival <10% in earlier era
- Indication for urgent liver transplantation
- Fascinating
- Frustrating
- Hard to treat
- Difficult to study

Classification of ALF Based on the Time Interval Between the Development of Jaundice and Encephalopathy

	Interval Between Onset of Encephalopathy from Jaundice	Common Etiologies	Clinical Presentation	Prognosis
Hyperacute	<7 days	APAP, HAV, ischemic	Cerebral edema common	Fair (survival without LT ~36%) ⁰
Acute	7-21 days	HBV, drugs	Cerebral edema less common	Poor (survival without LT ~14%)
Subacute	22 days to <26 weeks	Drugs, indeterminate	Cerebral edema rare; ascites, peripheral edema and renal failure more common	Very poor (survival without LT ~7%)

Abbreviations: APAP, acetaminophen; HAV, hepatitis A virus; HBV, hepatitis B virus; LT, liver transplantation.

Criteria for Characterization of Acute on Chronic Liver Failure (ACLF)

- Not acute liver failure
- Not decompensated cirrhosis
- ACLF is a unique form of
decompensated cirrhosis

Etiology of Acute Liver Failure

Etiology of Acute Liver Failure	
Infections	Viral hepatitis A, B, C, D, E Herpes simplex virus, varicella zoster virus Epstein-Barr virus, cytomegalovirus Tropical infections (eg, Dengue virus, leptospirosis, scrub typhus, malaria)
Drug and toxins	Acetaminophen Carbon tetrachloride Idiosyncratic drug reactions (eg, modern medications, a herbal supplements) Mushroom poisoning (eg, Amanita phalloides) Sea anemone sting
Ischemia	Ischemic hepatitis, hypoperfusion, cardiogenic shock Heat stroke Cocaine, methamphetamines, ephedrine, ecstasy
Vascular	Acute Budd-Chiari syndrome Sinusoidal obstruction syndrome
Miscellaneous	Autoimmune hepatitis Wilson disease Reye syndrome Malignant infiltration Acute fatty liver of pregnancy, eclampsia, HELLP syndrome Primary graft nonfunction after liver transplantation Indeterminate

Abbreviation: HELLP, hemolysis, elevated liver enzymes, low platelets.

a. Isoniazid, rifampicin, pyrazinamide, sulfonamides, trimethoprim-sulfamethoxazole, amoxicillin-clavulanate, dapsone, ketoconazole, ofloxacin, didanosine, efavirenz, allopurinol, diclofenac, halothane, isoflurane, phenytoin, valproic acid, nicotinic acid, statins, mipramine, propylthiouracil, disulfiram, lisinopril, labetalol, methyl dopa, amiodarone, flutamide, metformin, etoposide, gemtuzumab.

CAUSE

- Apoptosis
- Necrosis
- Cytokines
- Loss of oval cells
- Innate immunity
- Local factors
- DIC



Acute Liver Failure

Cerebral edema

Toxic cellular debris

No regeneration

Poor synthetic fxn

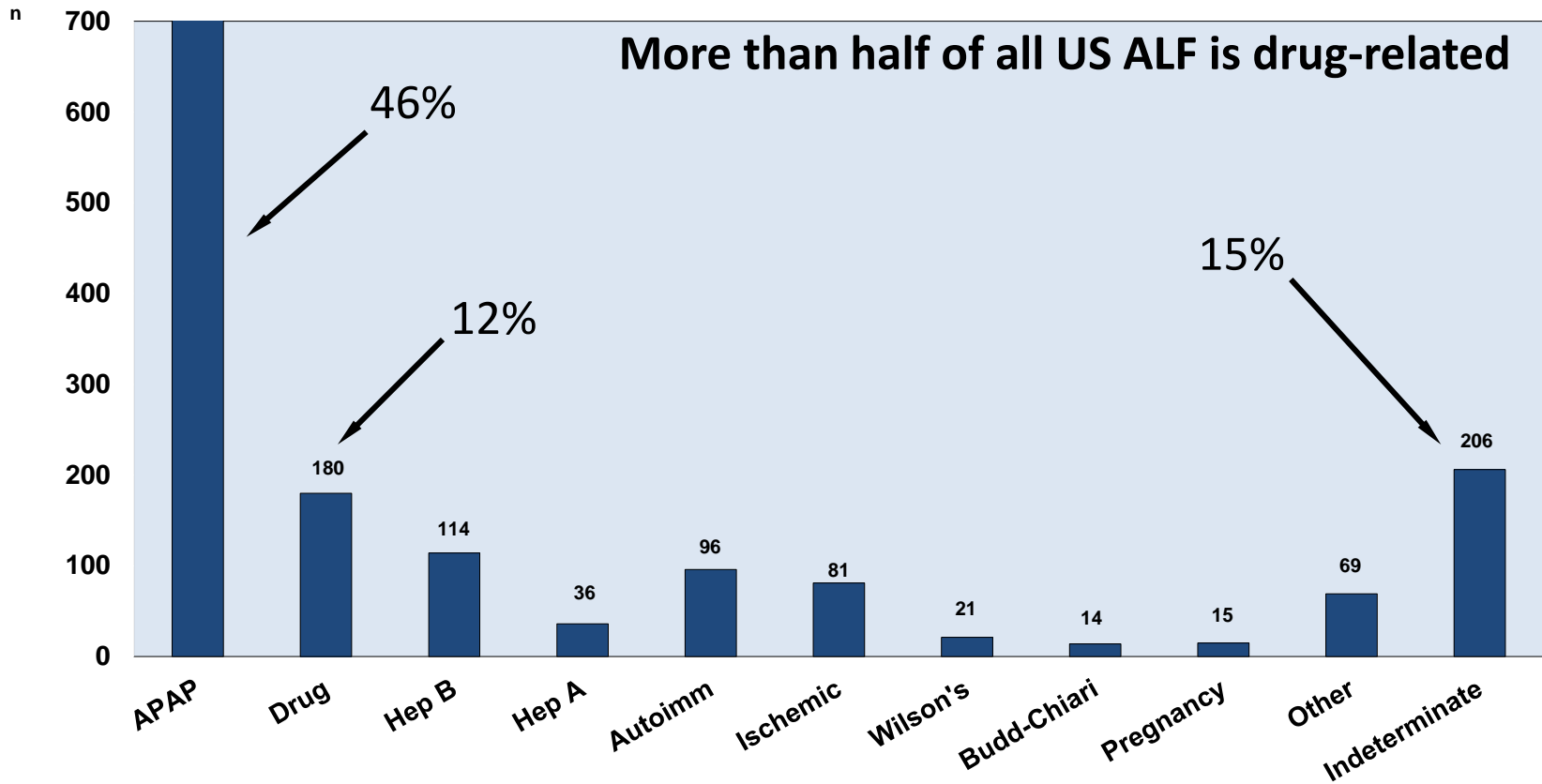
Poor toxin clearance

Increased infection risk

EFFECT

Etiology of ALF in the USA

Adult Registry (N=1,551)



Comparison of Different ALF Etiology Groups

N = 1,551

	APAP n=719	Drug n=180	Indeterminate n=206	HepA/HepB n=36/114	All Others N=296
Age (median)	37	47	38	49/42	44
Sex (% F)	75	67	59	47/44	73
Jaundice (Days) (median)	0	8	7	3/5	4
Coma \geq3 (%)	52	37	49	53/54	40
ALT (median)	3872	685	850	2124/1707	677
Bili (median)	4.4	20.3	22.0	12.5/18.5	14.4
Tx (%)	9	41	45	31/42	29
Spontaneous Survival (%)	67	29	26	56/25	39
Overall Survival (%)	74	68	68	83/61	65

Acute Hepatic Necrosis

- Sudden direct hepatotoxicity
 - ALT ↑ ↑ ↑, ALP & TB – N or ↑ (R ratio > 30)
 - AST often > ALT (predominant zone 3 injury)
 - INR may be elevated
 - Rapid improvement
- Patho: centrilobular necrosis
- D/Dx: ischemia, shock, hypothermia
- Causative agents: acetaminophen, CCl₄, phosphorous, poison mushroom, cocaine, ecstasy, amiodarone (IV), niacin & chemoRx

APAP Hepatotoxicity

- Worldwide leading cause of overdose and ALF
- Recommended dose: 325-1000 mg/dose; max 4 g/day
→ 325-650 mg/dose; max 3250 mg/day

Single overdose

- Ingestion > 7.5 to 10 g in adults
- Suicidal attempt ?

Repeated overdoses & therapeutic misadventure

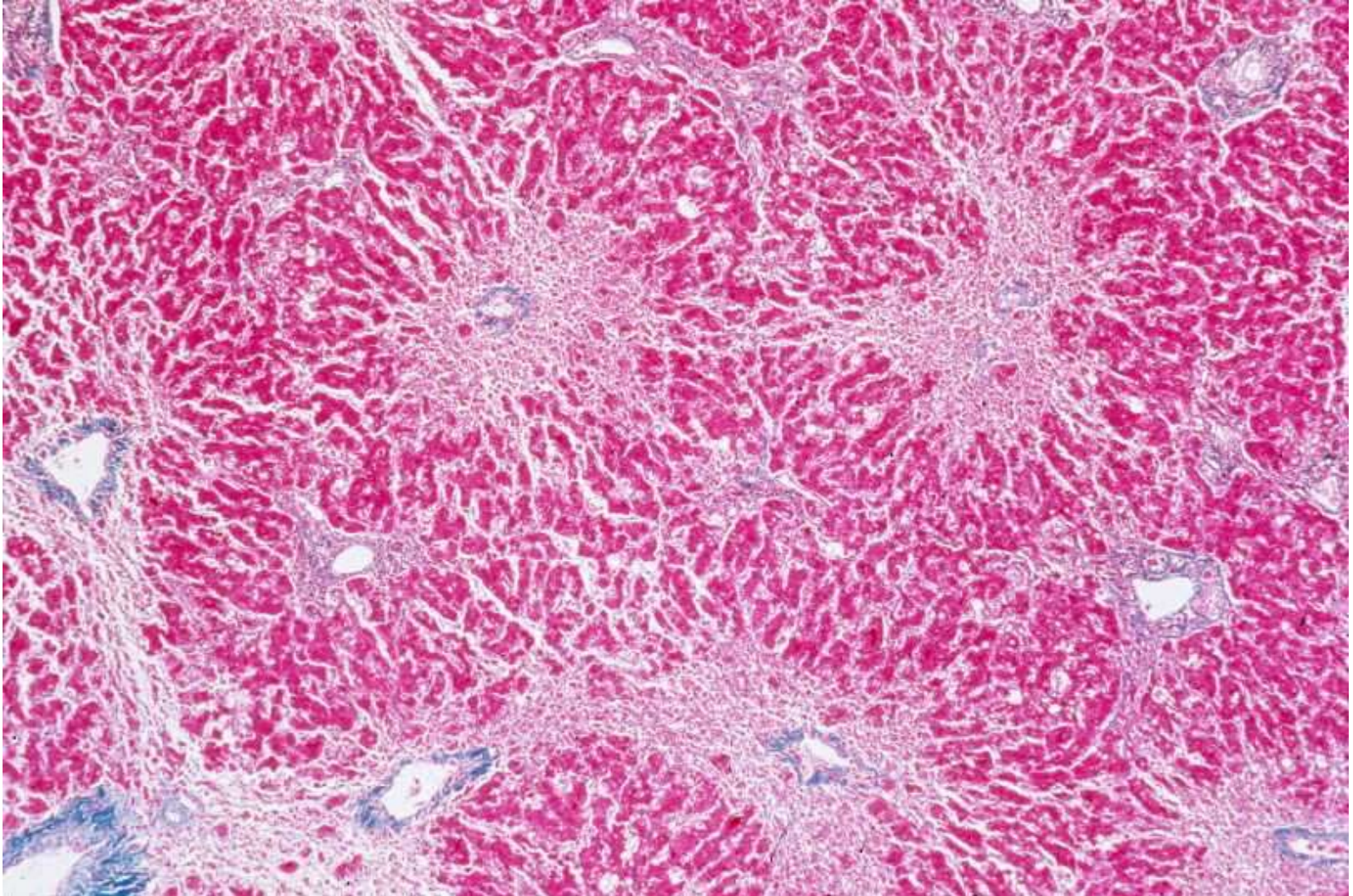
- Ingestions \geq 4-10 g/day esp. in high-risk populations
- Increasingly common (nowadays 30-50% of admitted APAP cases)
- Tend to present late; hepatotoxicity may have already evolved , sometimes difficult to diagnose → poorer prognosis

Acetaminophen Intoxication

	Accidental (N = 21)	Suicidal (N = 50)	P
Age	36	26	
Gender (F/M)	11/10	37/13	
Dose	12 (2–30)	20 (3-125)	0.009
Dose < 4gm	3 (14%)	2(4%)	
Acute ETOH	44%	39%	
Chronic ETOH	63%	29%	0.009
Peak ACM (mg/L)	7	126	<0.001
Peak ALT > 3500	52%	14%	0.002
Died	19%	2%	0.025

(Schiodt, et al. NEJM 1997; 337: 1112-17)

Acetaminophen Related Hepatotoxicity



ALF: Prognosis

King's College Criteria

- APAP
 - pH < 7.3
 - OR
 - All of the following
 - INR > 7
 - Cr > 3.4 mg/dL
 - Grade III or IV encephalopathy
- All other etiologies
 - INR > 7
 - OR
 - 3 of the following:
 - INR > 3.5
 - Age < 10 or > 40
 - Jaundice - encephalopathy > 7 days
 - Bilirubin > 17.5 mg/dL
 - Indeterminate ALF
 - Drug reaction

PPV: 70-100%

NPV: 25-94%

Prognosis in ALF: Etiology is a Main Determinant

Transplant free survival rates differ greatly

Good prognosis

- APAP 66%
- Ischemia 66%
- Pregnancy 55%
- Hepatitis A 56%

Bad prognosis

- Drugs 27%
- Indeterminate 25%
- Autoimmune 26%
- Hepatitis B 26%
- Wilson Disease 0%

*Age is NOT an important determinant

HAV-Related ALF: Clinical Study

- 29 HAV ALF patients:
 - 16 recovered, 9 OLT, 4 died
- Prognostic score used 4 features: ROC 0.899
 - ALT <2,600 IU/L
 - Cr >2.0
 - Intubation
 - Use of pressors
- ≥ 2 Factors has high predictive value
- Rate/yr declined from 5% to 0.7%

HBV-Related ALF

True Acute HBV ALF

Young

Caucasian

Better outcome

HBsAg negative

Low viral load

High IgM anti-HBc

Less e neg mutation

Chronic HBV ALF-likely HBVr

Old

Asian

Poor outcome

Never HBsAg neg

High viral load

Low IgM anti-HBc

All had e neg mutation

HBV-Related ALF (AFLSG)

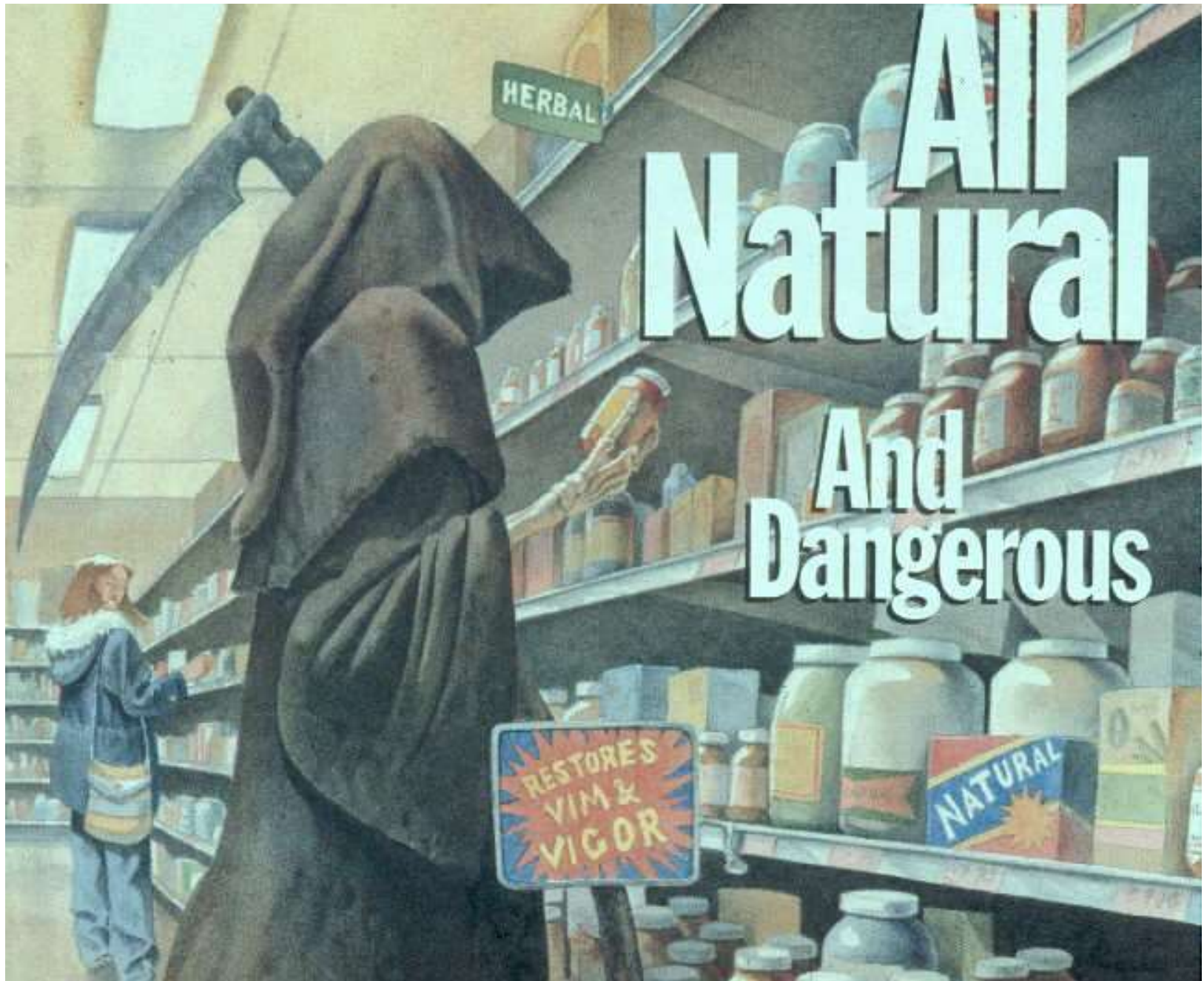
- At least two kinds of HBV ALF
- They behave quite similarly clinically but have different pathogenesis
- They appear to have different outcomes

Effect of nucleoside analogues is nil in ALF

Outcomes in True Acute ALF Patients

	NA- (n=35)	NA+(n=34)	P value
Overall Survival (%)	68.6	67.6	NS
Transplant (%)	31.4	47.1	NS
Spontaneous Survival (%)	37.1	23.5	NS

Herbal Preparations and ALF



All
Natural

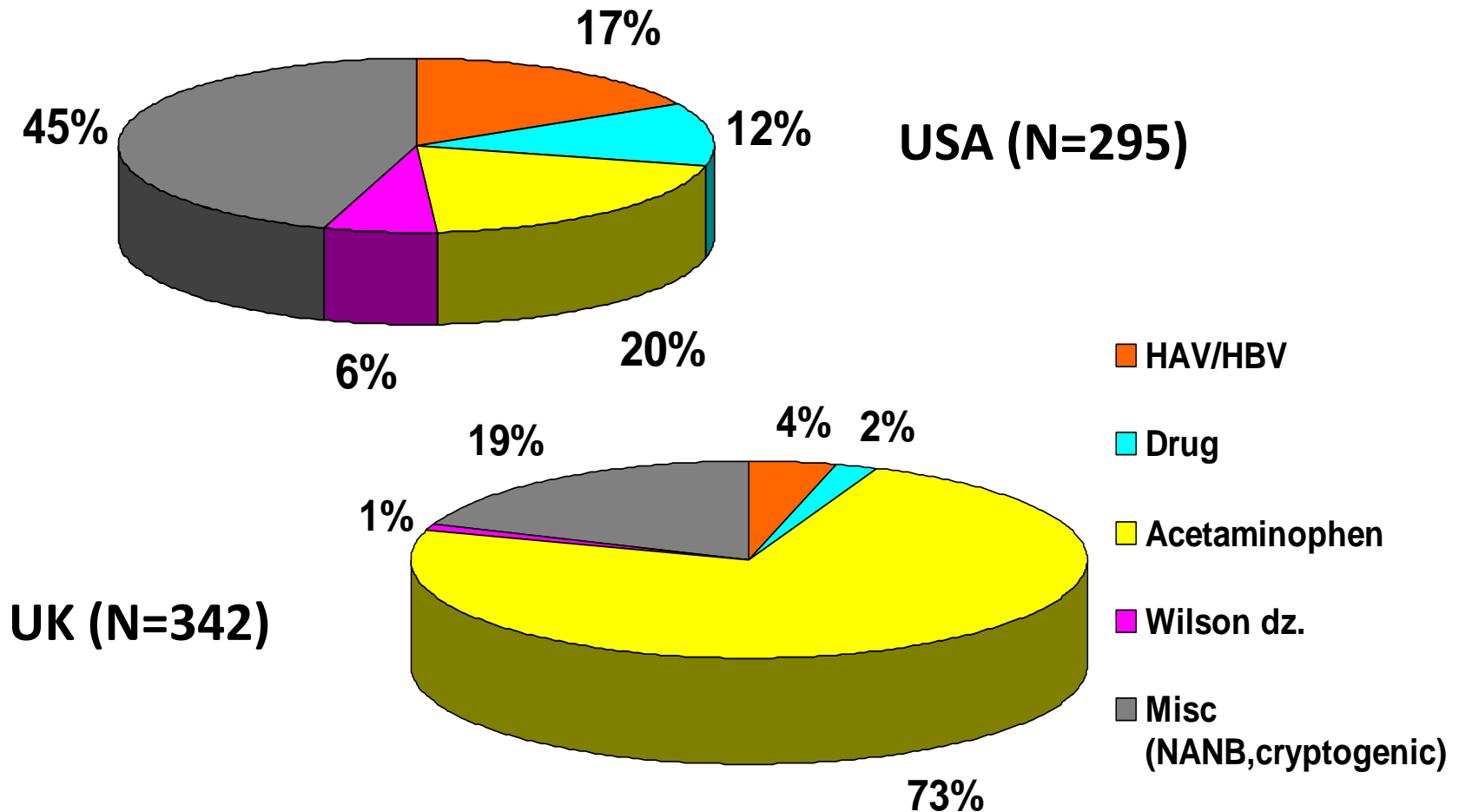
And
Dangerous

HERBAL

RESTORES
VIM &
VIGOR

NATURAL

Acute Liver Failure: Etiologies According to Countries



Most Frequent Agents Causing ALF

Agents	N (total = 137)
Antibiotics <ul style="list-style-type: none">• INH• Sulfa• Nitrofurantoin• Azoles• Others	20 10 10 3 13
Anticonvulsants <ul style="list-style-type: none">• Phenytoin• Others including psychotropics	8 10
Herbs	11
Others <ul style="list-style-type: none">• PTU, troglitazone, bromfenac, methyldopa	4 or more cases

Ma-Huang

- Derived from *Ephedra spp.*
- Sympathomimetic drug
- Used for cough, nasal and sinus congestion, asthma
- Increase metabolic activity
 - Aid to weight loss
- Types of liver injury
 - Hepatitis
 - Acute liver failure
 - Autoimmune hepatitis



Jin Bu Huan (*Lycodium serratum*)



- Used for more than 1000 years as a sleeping aid and analgesic
- Types of liver injury
 - Acute hepatitis
 - Mean duration 20 weeks after taking
 - Peripheral eosinophilia may be seen
 - Chronic hepatitis
 - Histology – periportal focal necrosis and fibrosis, cholestasis, lymphocytic infiltrates, microvesicular steatosis
 - Cholestasis

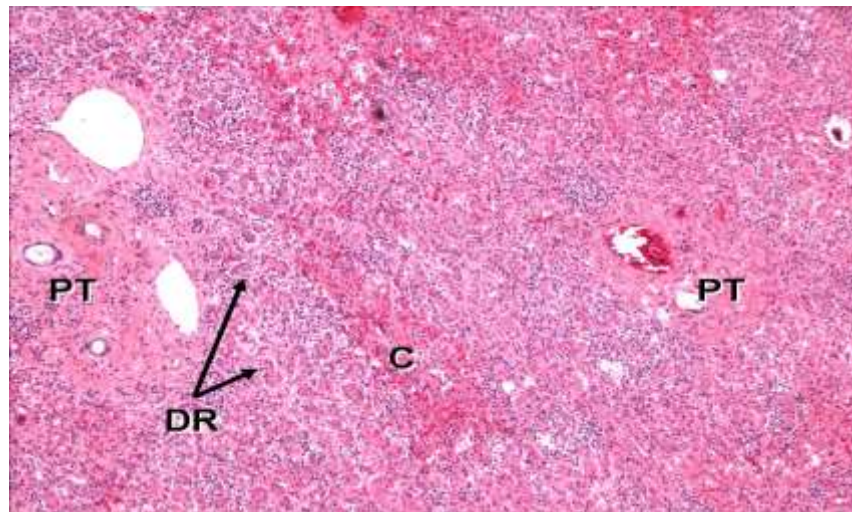
(1) Horowitz RS, et al. Arch Intern Med 1996;156:899-903

(2) Woolf GM, et al. Ann Intern Med 1994;121:729-35

(3) Schiano TD. Clin Liver Dis 1998;2:607-630

Black Cohosh Hepatotoxicity: Mimics Autoimmune Hepatitis

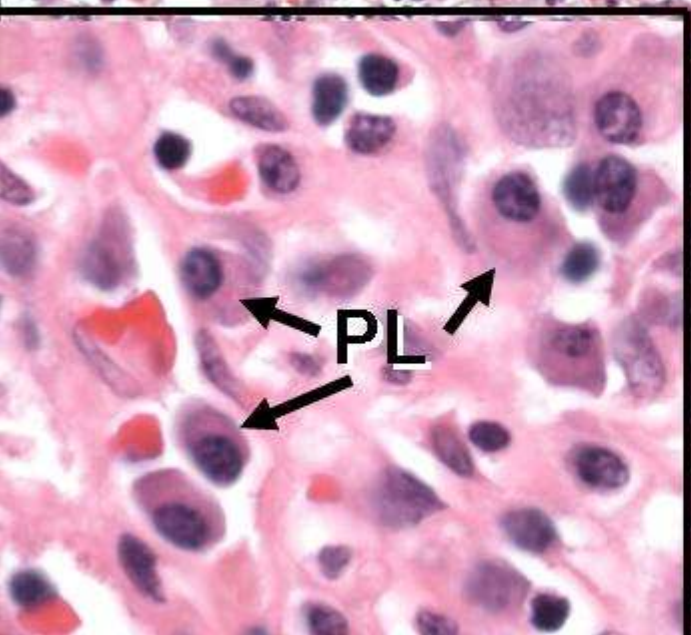
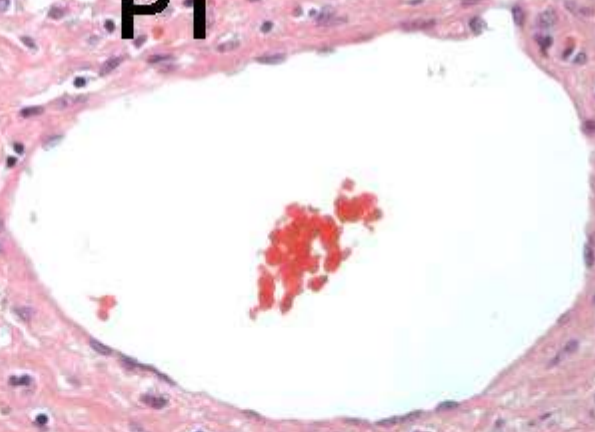
- 35 yo woman, began a mail order pill one/day
- Admitted 4 wks later with coma
- TB 19.3, AST 835/ALT 674, INR 3.9, ANA 1:640
- Transplantation required



Interface Hepatitis



PT

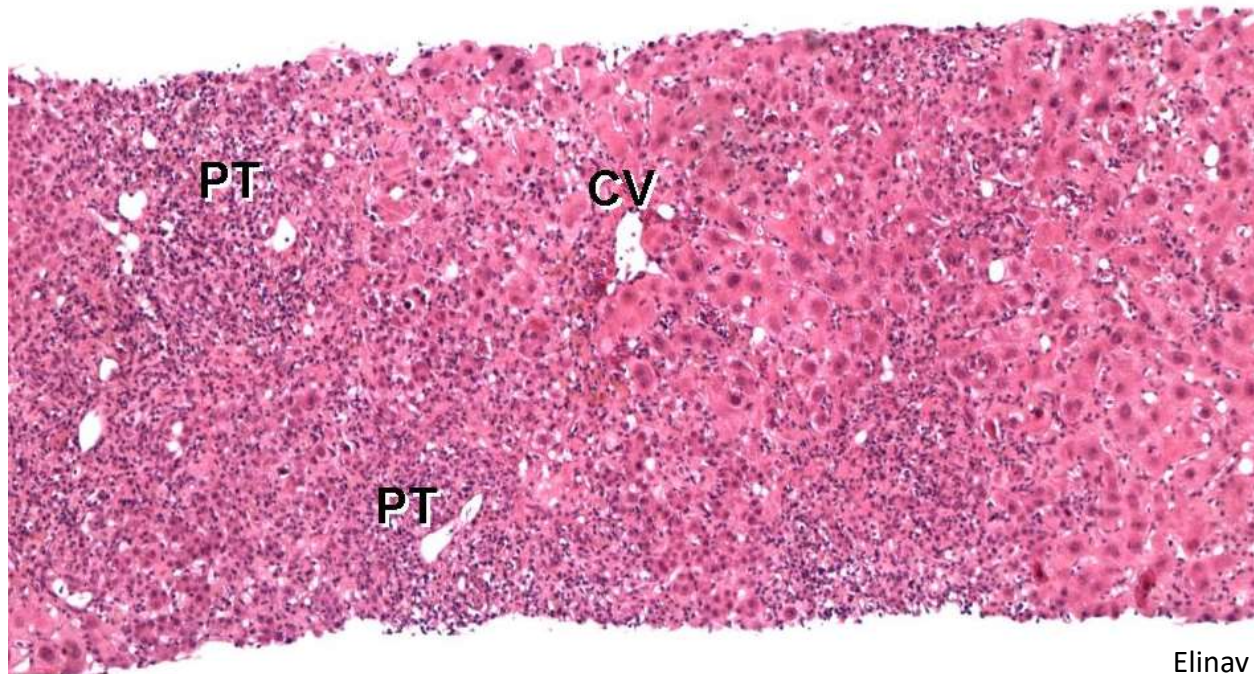


PL



Herbalife[®] Hepatotoxicity

- 38 yo housewife, took 3 tab/day as tea for 3 weeks for weight loss
- Noted nausea, dark urine, jaundice
- Two wks later: TB 14.2, AST 2,624, INR 1.9
- Recovered after drug withdrawn



Hydroxycut®

- Energy enhancer and fat burner
- Dietary supplement used for weight loss
- Severe liver injury reported



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Public Health Focus

Hydroxycut Products

Updated: May 8, 2009

Background

The U.S. Food and Drug Administration (FDA) is warning consumers to immediately stop using Hydroxycut products by Iovate Health Sciences, Inc., of Oakville, Ontario and distributed by Iovate Health Sciences U.S.A., Inc. of Blasdell, NY. Hydroxycut products are associated with a number of serious liver injuries.

The FDA has received 23 reports of serious health problems ranging from jaundice and elevated liver enzymes, an indicator of potential liver injury, to liver damage requiring liver transplants. One death due to liver failure has been reported to FDA. Other health problems reported include seizures; cardiovascular disorders; and rhabdomyolysis, a type of muscle damage that can lead to other serious health problems such as kidney failure.

Therapy for ALF

ALF: Management Considerations

- INR \geq 1.5 requires admission
 - ICU or step-down with mental status changes
- Transfer early if not a transplant center
 - Initiation of transfer at Grade I-II encephalopathy

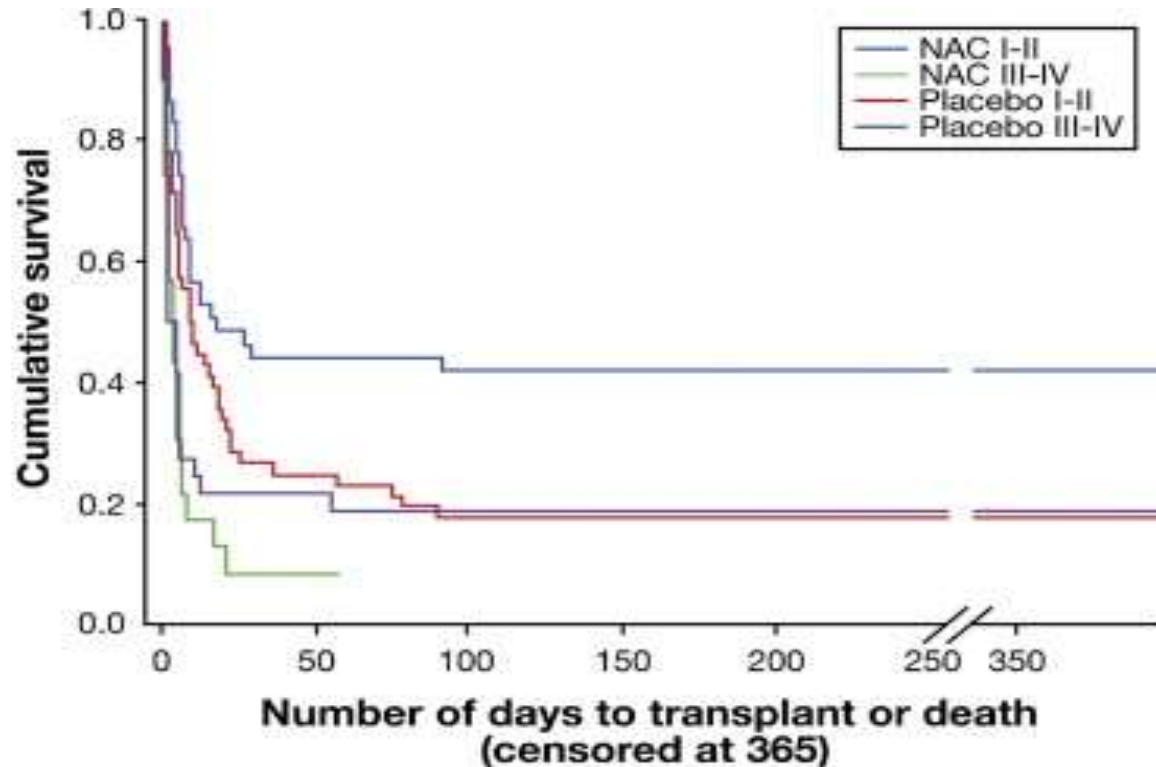
ALF: Etiology Specific Therapies

- Etiology

- Acetaminophen N-Acetyl Cysteine
- Amanita phalloides PCN; silymarin
- Acute fatty liver of pregnancy Delivery
- HSV Acyclovir
- Autoimmune Steroids
- Budd-Chiari Heparin/TIPS

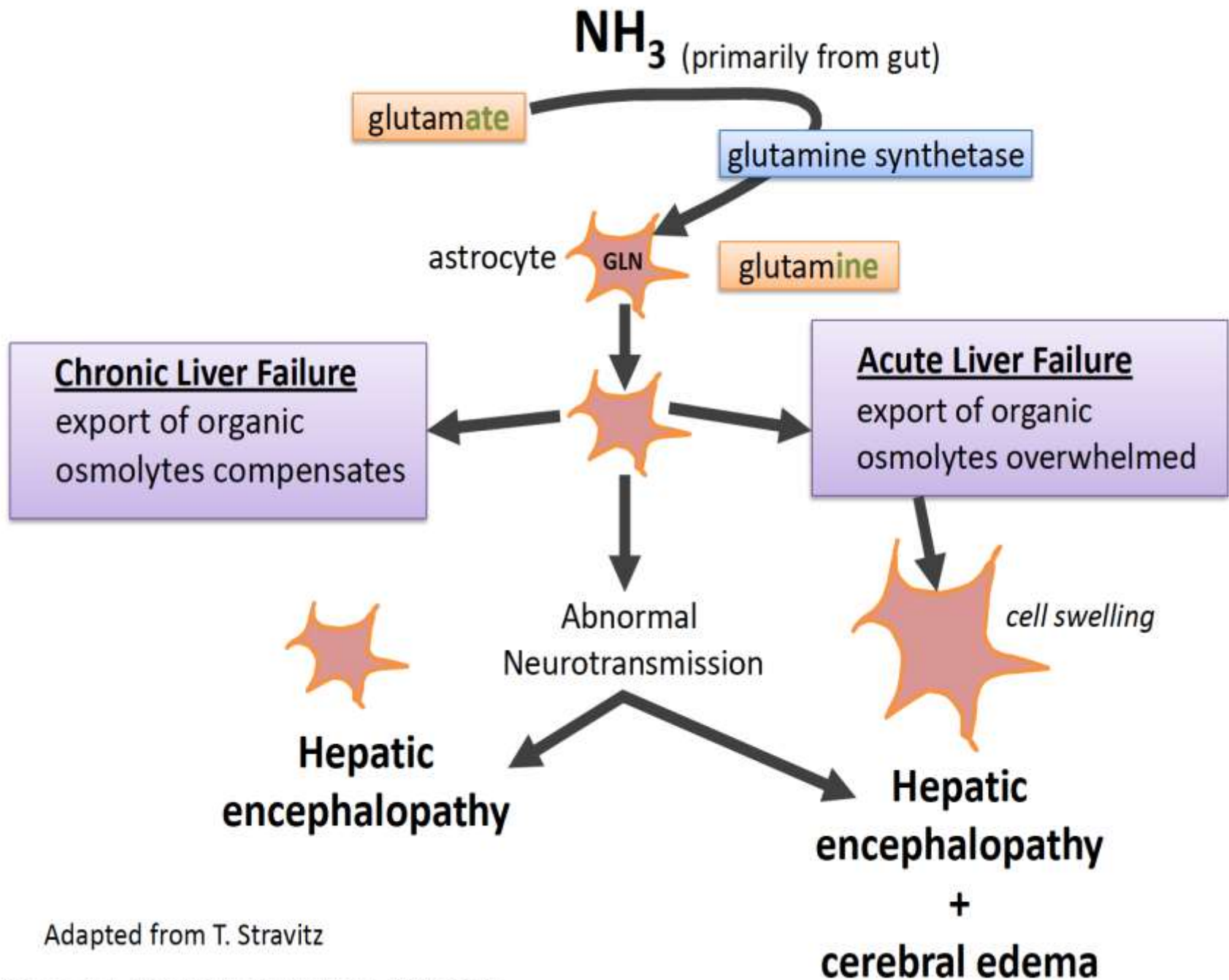
ALF: Etiology Specific Therapies

- IV NAC improves transplant free survival in early stage non-APAP ALF



ALF: Complications

- Hepatic Encephalopathy
- Intracranial Hypertension/ Cerebral Edema
- Infection
- Shock/ Multi-organ System Failure
- Coagulopathy
- Acute Kidney Injury



Adapted from T. Stravitz

ALF: Cerebral Edema

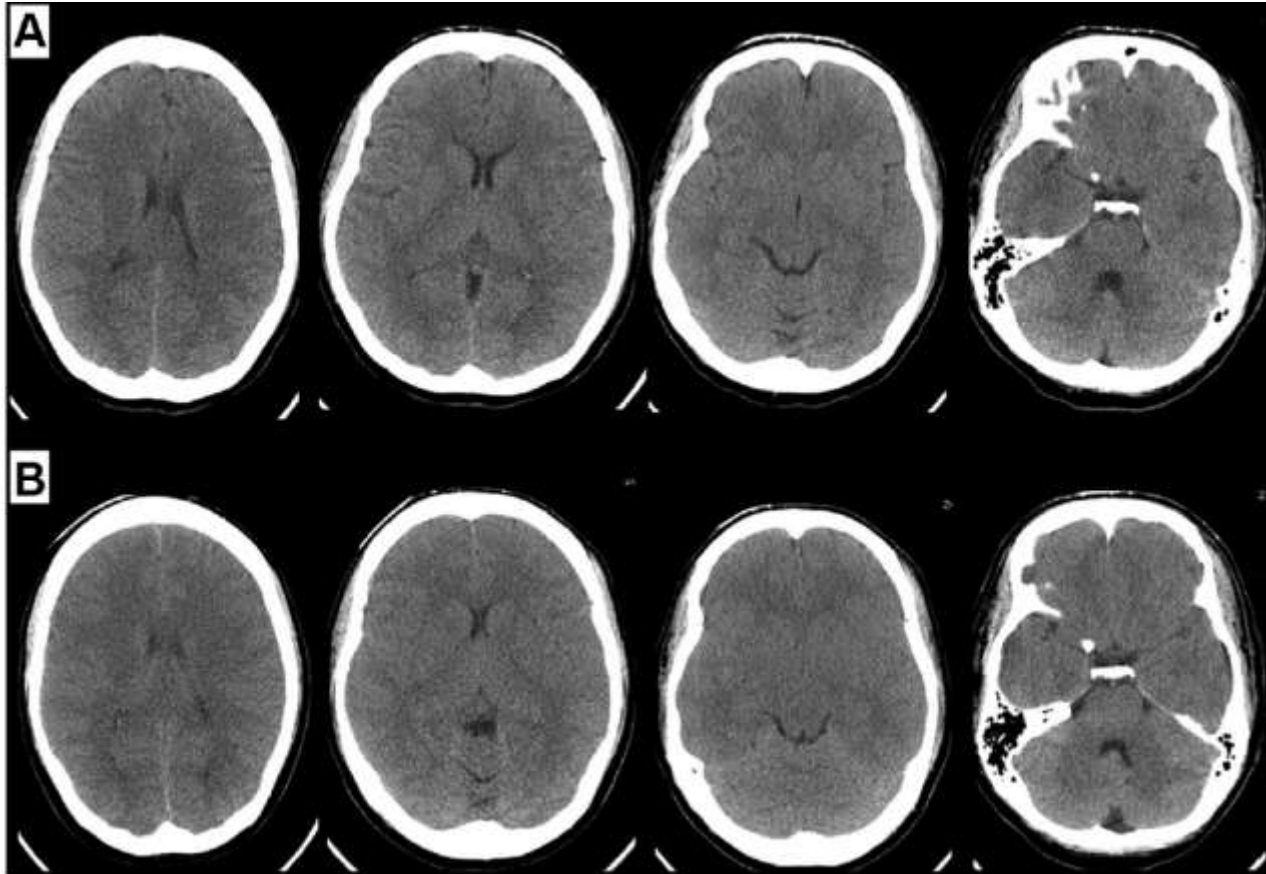
- Develops in 75-80% of patients with grade IV HE
- Osmotic derangements in astrocytes and alteration in cellular metabolism
- Elevated ICP and brainstem herniation are the most common causes of death

ALF: Cerebral Edema

General Management

- Head CT with changes in mental status
- Intubation for grade III/IV encephalopathy
- Frequent neuro checks
- HOB elevated to 30 degrees
- Avoidance of stimulation
- ICP monitoring
 - Not performed at all institutions
 - Transcranial dopplers and EEG may be helpful
 - Findings on CT scan represent late findings

Features of CE with or without signs of herniation may be observed on CT scans



(A) Computed tomography (CT) scan of the brain of a patient with acute liver failure and grade III encephalopathy showed mild cerebral edema with loss of sulci and gyri, blurring of grey-white junctions and mild narrowing of ventricles. (B) CT of the brain of the same patient (5 days later) showed progression of cerebral edema and impending brain herniation.

ALF: Cerebral Edema

General Management

- Intracranial Hypertension (ICP > 20 mmHg)
 - Hyperventilation
 - Goal PaCO₂ 25-30 mm Hg
 - Mannitol
 - 0.25-2g/kg
 - Carries risk of volume overload
 - Hypertonic Saline
 - 3%, Serum sodium goal of 145-155
 - Hypothermia
 - 32-34 degrees Celsius

ALF: Infection

General Management

- Patients with ALF are at increased risk of infection due to immunologic derangements
- Role of prophylactic antibiotics is controversial
- Antibiotics recommended in patients with rapid progression of HE, refractory hypotension, and SIRS
- Low threshold to add antifungals if refractory shock

ALF: Multi-organ System Failure

General Management

- Shock/ Multi-organ System Failure
 - Fluid replacement with colloid favored
 - MAPs > 75/ CPP 60-80 mmHg
 - Norepinephrine +/- vasopressin for management of hypotension
 - CVVHD if RRT needed

ALF: Coagulopathy

General Management

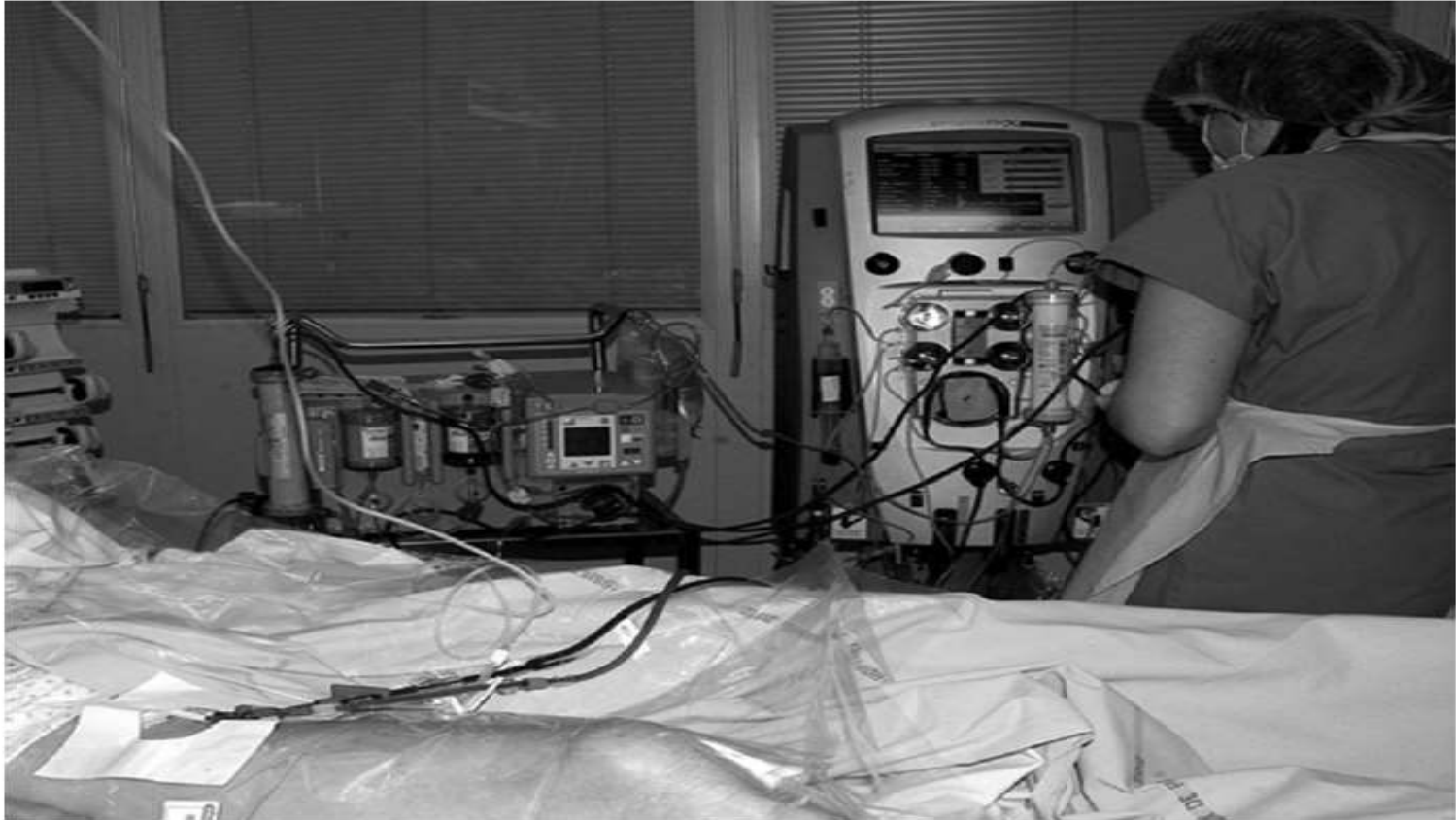
- Severe coagulopathy increases risk for spontaneous bleeding
 - GI tract most common site
- Prophylactic FFP not recommended
 - No survival benefit
 - May worsen cerebral edema
- Trial of vitamin K recommended
- rFVIIa associated with normalization of PT and control of bleeding but increased risk of thromboses

ALF: Acute Kidney Injury

General Management

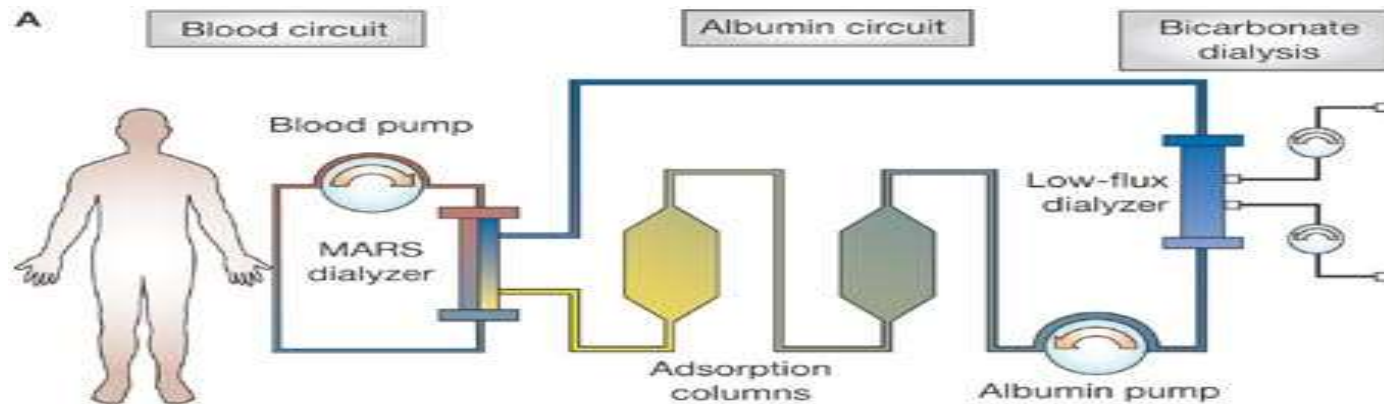
- Observed in up to 75% of patients with ALF
- Due to hepatorenal syndrome, ATN
- Maintain adequate systemic blood pressure, avoid nephrotoxins

The MARS Dialysis Machine



Saliba, F. et al. *Annals of Internal Medicine*;159:522-31

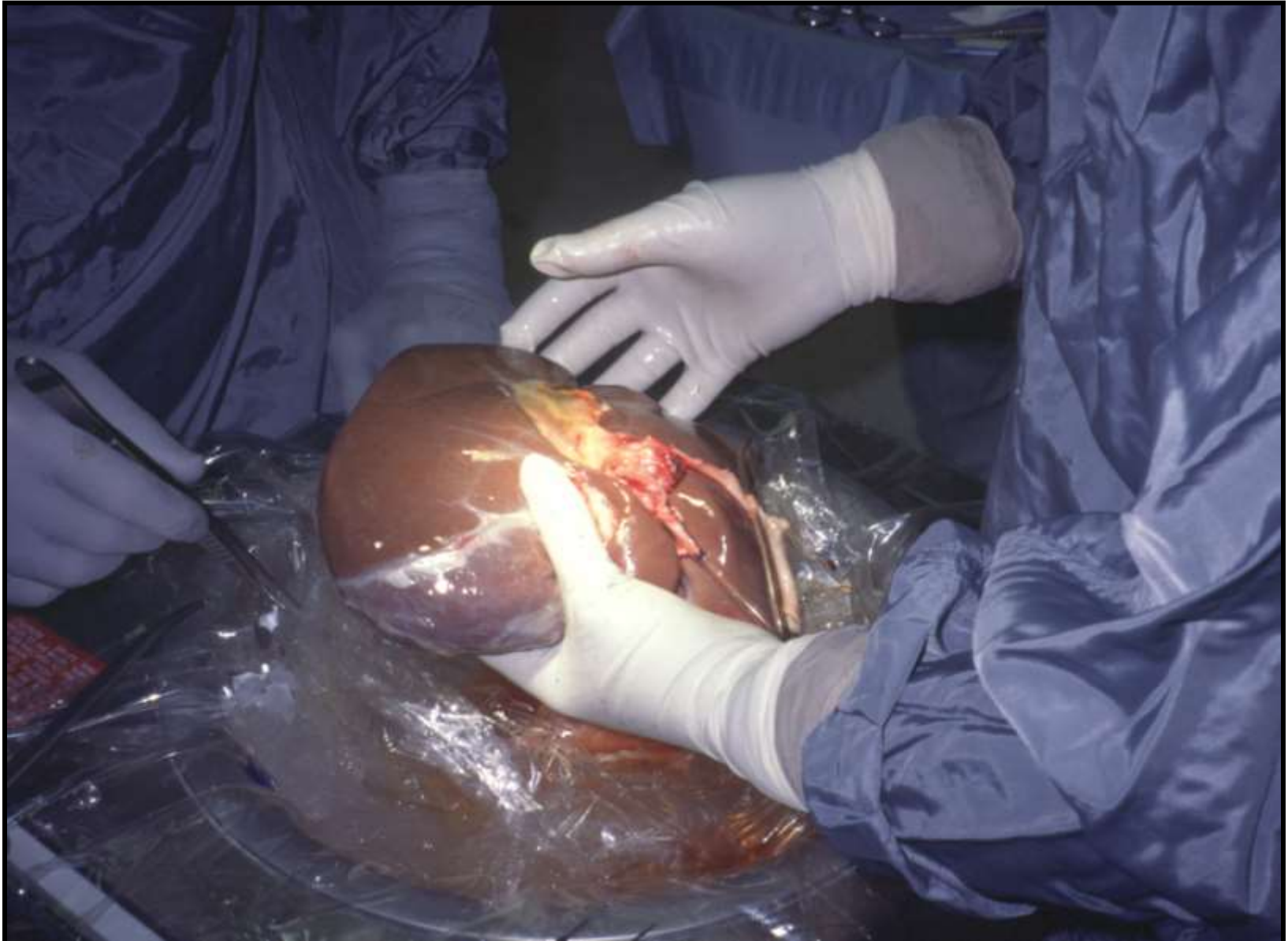
Molecular Adsorbent Recirculating System (MARS)



Artificial Liver Support: Current Status 2017

- HELIOS study (Prometheus): 145 patients “ACLF”. Survival benefit only if MELD >30 or HRS. No overall survival benefit
- RELIEF study (MARS-molecular adsorbent recirculating system) 189 patients with ACLF. No survival benefit
- MARS ALF study (France): No survival benefit. Liver transplants within 16 hours of listing!

Liver Transplantation

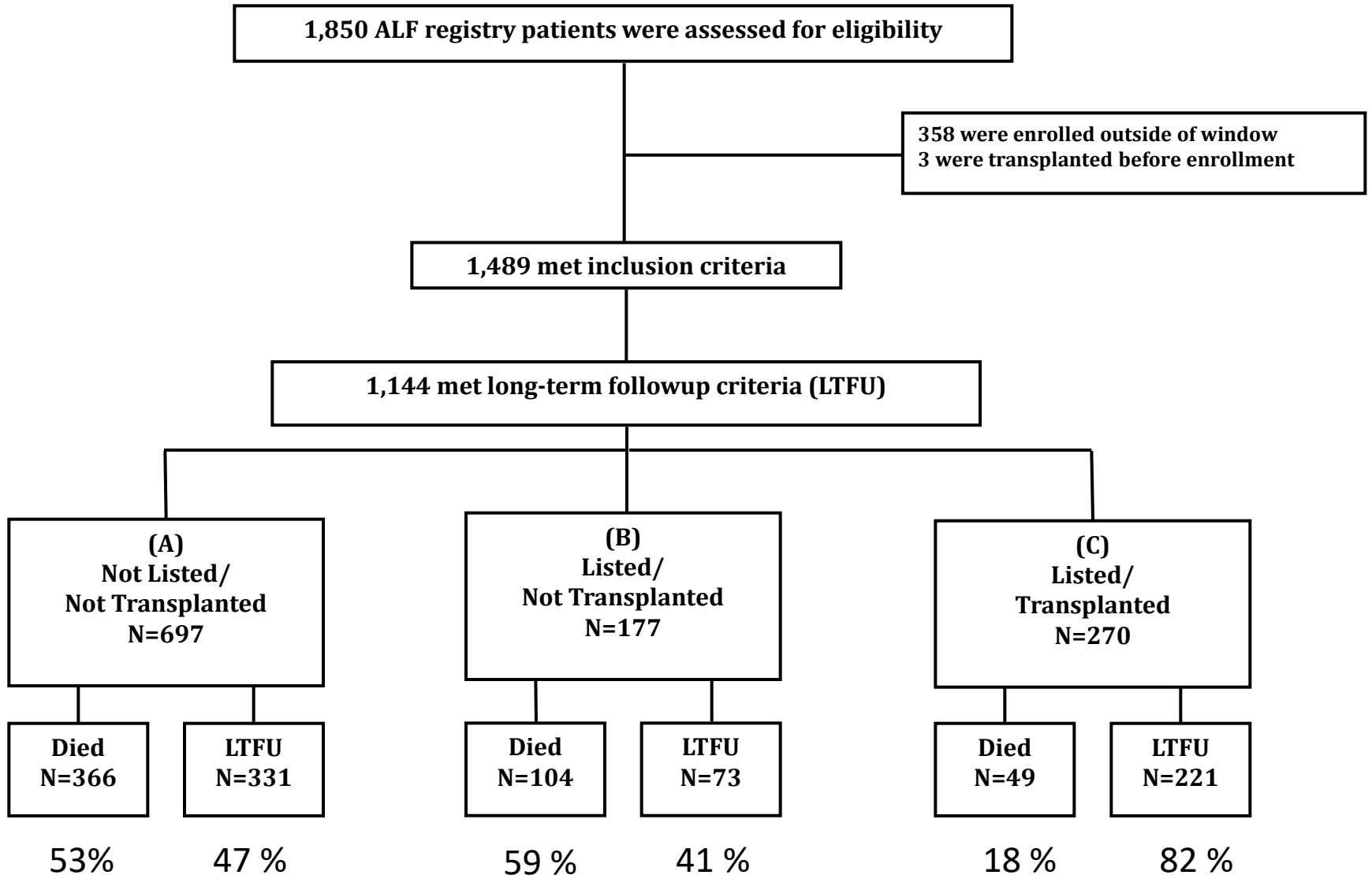


ALF: Liver Transplantation

- Contraindications
 - Severe irreversible brain damage
 - Severe hypoxia
 - CPP < 40 mmHg for > 2 hrs
 - Sustained elevation ICP > 50 mmHg
 - Septic shock
 - Severe cardiopulmonary disease
 - AIDS

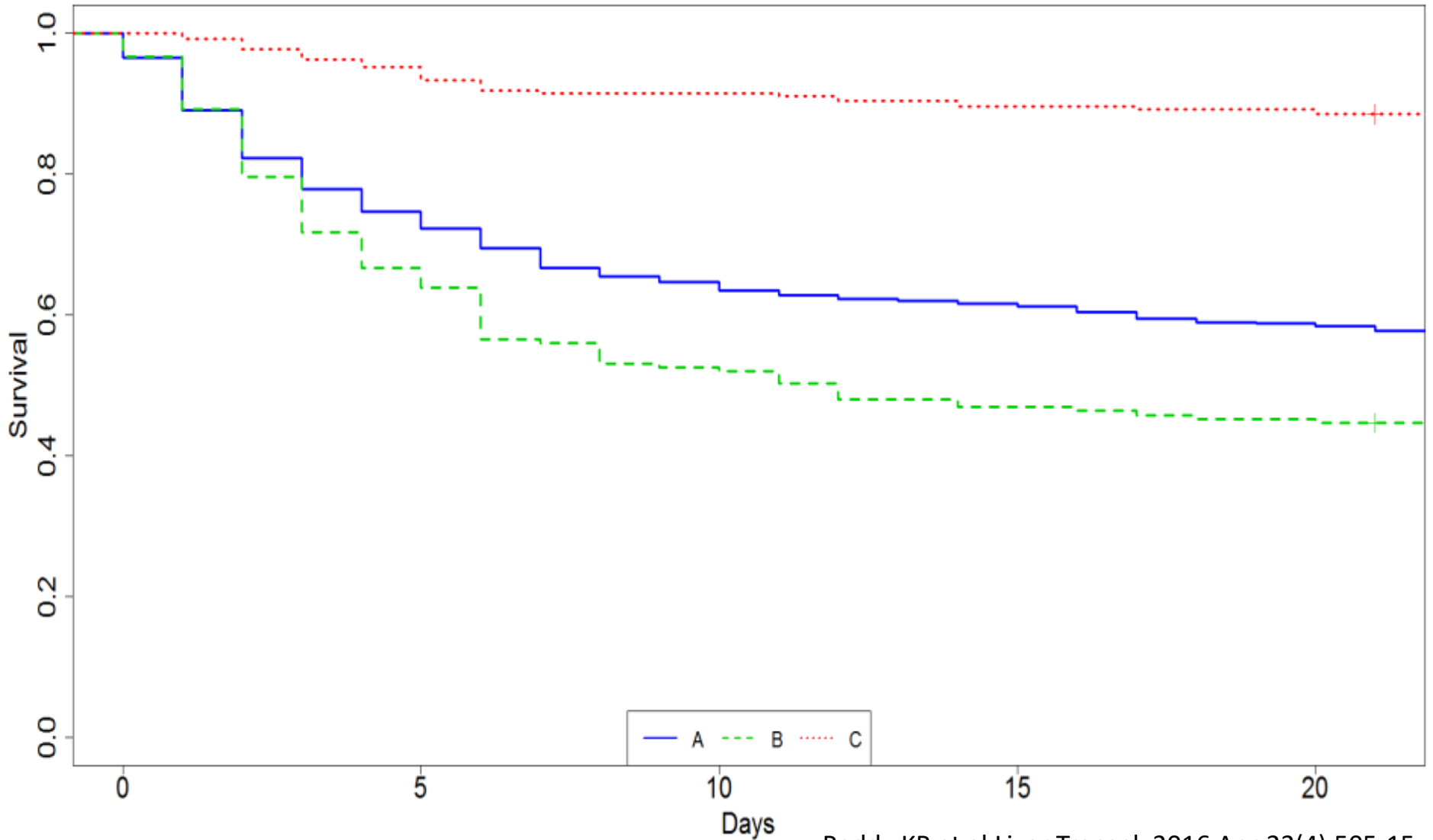
Results

Study Population



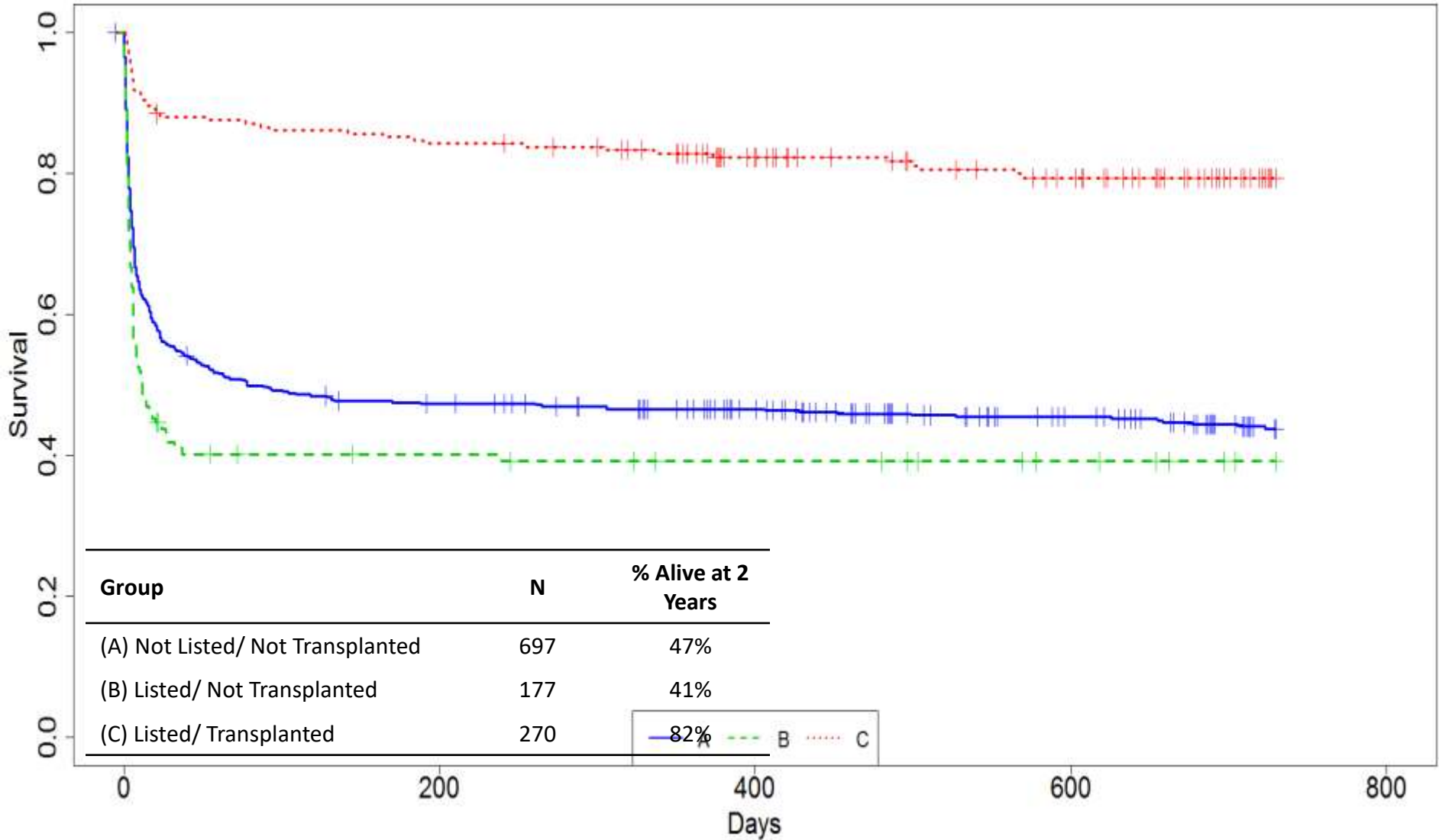
Survival

21 Day Survival



Survival

Two-Year Survival



ALF: Summary

- ALF, because of its rarity and multiple etiologies, presents numerous management challenges
- Etiology specific therapy and consideration for liver transplantation should be entertained early
- Patients with ALF should be managed at LT centers with experienced providers to maximize outcomes