ACUTE HEPATIC FAILURE
(Prognosis & Liver transplantation)

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Definition

- Complex syndrome of acute liver injury with $\text{INR}>1.5$ and any degree of encephalopathy in a patient without preexisting cirrhosis
- Duration of illness less than 26 weeks
- Fulminant liver failure: duration less than 8 weeks

Exceptions for preexisting cirrhosis:
- Wilson’s disease
- Vertically transmitted hepatitis B
- Autoimmune hepatitis
Introduction

- Acute liver failure (ALF) is a rare condition in which rapid deterioration of liver function results in altered mentation and coagulopathy in previously normal individuals.

- The most prominent causes include drug induced liver injury, viral hepatitis, autoimmune liver disease and shock or hypoperfusion; many cases (20%) have no discernible cause.

- Paracetamol remains the most common aetiology of acute liver failure in developed countries, whereas acute viral aetiologies predominate elsewhere.
Acute liver failure in USA

- Actaminophen overdose (46%)
- Indeterminant (14%)
- Drug related (11%)
- HBV (7%)
- Autoimmune hepatitis (5%)
- Ischemia (4%)
- HAV (3%)
- Wilson (2%)
- Other causes (7%)
Acute Liver Failure in Spain: Analysis of 267 Cases

Àngels Escorsell,¹,² Antoni Mas,¹,² Manuel de la Mata,³ and the Spanish Group for the Study of Acute Liver Failure*

- 267 patients in 17 hospitals from 1992-2000
- Viral hepatitis in 37% (mostly HBV)
- Unknown cause in 32%
- Drug and toxins in 19% (acetaminophen in 2%)
- Overall survival 58%.

Liver Transplantation 2007;13:1389-95
prognosis

- Cause is one of the most important predictors of ALF Outcome.

- The lowest mortality is seen with APAP hepatotoxicity (30%) and hepatitis A virus (50%). In contrast, the mortality in the remainder of causes is abysmal (80–100%).

- Paradoxically, those with more rapid development of hepatic encephalopathy appear to have a better outcome compared with those with a longer interval between development of symptoms and encephalopathy. (1)

(1) Anne M. Larson; Diagnosis and management of acute liver failure; Current Opinion in Gastroenterology 2010.
Outcome Based on Days of Symptoms Prior to Occurrence of Encephalopathy

- Hyperacute (0-7 days)
  - Transplant free survival 30%
- Acute (7-28 days)
  - Transplant free survival 33%
- Subacute (>28 days)
  - Transplant free survival 14%
Prognosis (Con’t)

- Prognostic scoring systems, although derived from data on relatively large numbers of patients, still fail to achieve success, given the wide variety of etiologies that lead to this end stage syndrome.

- The traditional King’s College Hospital criteria have been the most commonly utilized & most frequently tested of the numerous propose prognostic criteria for ALF. (PPV<70% to 100% & NPV:25-94%)
Prognostic Factors: King’s College Criteria

Acetaminophen cases
- Arterial PH < 7.3 or
- Arterial lactate > 3.5 at 4 hrs or
- Arterial lactate > 3 at 12 hrs or
  - INR > 6.5 &
  - Cr > 3.4 &
  - Stage 3 or 4 encephalopathy

Non-acetaminophen cases
- INR > 6.5 or
- Any 3 of the followings:
  - Age < 10 or > 40 yrs
  - Duration of jaundice > 7 d
  - Total Bili > 17.5
  - INR > 3.5
  - Etiology: idiosyncratic drug, halothane, idiopathic, non-A non-B hepatitis

*Lancet 1993;342:273-5*
<table>
<thead>
<tr>
<th>King's College Hospital criteria* for liver transplantation in fulminant hepatic failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acetaminophen-induced disease</strong></td>
</tr>
<tr>
<td>Arterial pH &lt;7.3 (irrespective of the grade of encephalopathy)</td>
</tr>
<tr>
<td><strong>OR</strong></td>
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<tr>
<td>Grade III or IV encephalopathy AND</td>
</tr>
<tr>
<td>Prothrombin time &gt;100 seconds AND</td>
</tr>
<tr>
<td>Serum creatinine &gt;3.4mg/dL</td>
</tr>
<tr>
<td><strong>All other causes of fulminant hepatic failure</strong></td>
</tr>
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<td>Prothrombin time &gt;100 seconds (irrespective of the grade of encephalopathy)</td>
</tr>
<tr>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>Any three of the following variables (irrespective of the grade of encephalopathy)</td>
</tr>
<tr>
<td>1. Age &lt;10 years or &gt;40 years</td>
</tr>
<tr>
<td>2. Etiology: non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions</td>
</tr>
<tr>
<td>3. Duration of jaundice before onset of encephalopathy &gt;7 days</td>
</tr>
<tr>
<td>4. Prothrombin time &gt;50 seconds</td>
</tr>
<tr>
<td>5. Serum bilirubin &gt;18 mg/dL</td>
</tr>
</tbody>
</table>

* A statistical model for predicting the outcome in patients with FHF
Prognosis (Con’t)

- **King's College Hospital Criteria (KCHC)** had its greatest specificity and PPV in patients with acetaminophen overdose.

- This model has great specificity and positive/negative predictive value, but poor sensitivity.
Modified criteria of KCH for paracetamol acute liver failure etiology

<table>
<thead>
<tr>
<th>Strongly consider listing for OLT if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial lactate &gt;3.5 mmol/L after early fluid resuscitation</td>
</tr>
</tbody>
</table>

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<tr>
<th>List for transplantation if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pH &lt;7.3, or arterial lactate &gt;3.0 mmol/L after adequate fluid resuscitation</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>List for transplantation if all 3 of the following occur within a 24-h period:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade III–IV HE</td>
</tr>
<tr>
<td>PT &gt;100 s (INR &gt;6.5)</td>
</tr>
<tr>
<td>Serum creatinine &gt;300 mcmol/L</td>
</tr>
</tbody>
</table>
Factors Predictive of Survival & Neurological Sequel

- 500 pts with ALF (350 with FHF) from 1986-2006
- 150 pts had no HE, 98% survived
- Cause of death: cerebral edema (44%), sepsis (29%)
- Compared two groups of pre and post 1996
  - Lower rate of HBV related, stage IV HE & brain death
  - Higher rate of acetaminophen related, better post OLT survival
- Controlled for hepatic coma & organ failure, better outcome was secondary to earlier ICU admission & less HBV infection

EASL annual meeting, April 2007
Potentially helpful indicator of good (transplant free) prognosis in patient with ALF

- 1: acetaminophen
- 2: ischemia
- 3: HAV

(58-64%)
Potentially Helpful Indicators* of Poor (Transplant free) Prognosis in Patients With ALF

Etiology

- Idiosyncratic drug injury
- Acute hepatitis B (and other non-hepatitis A viral infections)
- Autoimmune hepatitis
- Mushroom poisoning
- Wilson disease
- Budd-Chiari syndrome
- Indeterminate cause (20-25%)

Coma grade on admission

- III
- IV
Results of a Prospective Study of Acute Liver Failure at 17 Tertiary Care Centers in the United States

George Ostapowicz, MD; Robert J. Fontana, MD; Frank V. Schiodt, MD; Anne Larson, MD; Timothy J. Davern, MD; Steven H.B. Han, MD; Timothy M. McCashland, MD; A. Obaid Shakil, MD; J. Eileen Hay, MD; Linda Hynan, PhD; Jeffrey S. Crippin, MD; Andres T. Blei, MD; Grace Samuel, MS; Joan Reisch, PhD; William M. Lee, MD; and the U.S. Acute Liver Failure Study Group*

- 308 pts in 17 centers
- Median age 38 yrs
- 73% women
- 39% acetaminophen toxicity
- 13% Idiosyncratic drug toxicity
- 17% undetermined
- 12% hepatitis B & A

52%
other score

- Viral (clichy score) age < 30
  factor V < 20%, grade 3 to 4 encephalopathy
- MELD score (MELD > 30)
- APACHE II (score > 15)
- Ammonia level (all) > 150-200 umol/L
- A fetoprotein (acetaminophen) AFP < 3.9 ug/L day 1
## Alternative prognostic variables suggested for use in acute liver failure

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<th>Prognostic variable</th>
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<td>HE + Factor V &lt; 20% (age &lt;30 year) or &lt;30% (age &gt;30 year)</td>
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</tr>
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In a study of 127 patients with ALF, serum ferritin was measured on days 1 & 3 after hospitalization.

Patients who spontaneously survived (n = 64) had larger median reductions in serum ferritin from day 1 to 3 compared with those who underwent OLT (n=32) (p<0.05) or those who died without OLT (n=31) (p<0.0001).

This study concluded that Patients with initial levels of serum ferritin greater than 20,000 mcg/L have a high probability of survival without OLT.

Significant reductions of serum ferritin during the initial course of ALF likely indicate return of liver function.(1)

(1) Jessica D. Korman, Frank V. Schiodt, and et al; Elevation of Serum Ferritin and Survival of Patients with Acute Liver Failure, Gastroenterology, Volume 124, Issue 4, Supplement 1, April 2003, Page A756
Treatment efficacy

Highly effective:

1: (N-acetylcysteine in acetaminophen toxicity,
2: Promt delivery in AFL of pregnancy & HELP
3: penicillin G in Amanita toxicity
Efficacy of treatment

- Less effective

1: Acyclovir in herpes virus
2: Steroid in autoimmune hepatitis
3: Nucleoside analogue in hepatitis B
Prognosis (con’t)

- In patients with ALF, there were no significant differences in survival or rate of liver transplantation among racial and ethnic groups except for transplantation in Hispanics. (1)

- Data published in Gastroenterology indicate that intravenous NAC improves transplant-free survival in patients with early stage non-acetaminophen-related acute liver failure. However, patients with advanced coma grades do not benefit from NAC and typically require emergency liver transplantation. (2)

(1) KIMBERLY A. FORDE, K. RAJENDER REDDY, ANDREA B. TROXEL and the ACUTE LIVER FAILURE STUDY GROUP; Racial and Ethnic Differences in Presentation, Etiology, and Outcomes of Acute Liver Failure in the United States, CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2009;7:1121–1126
(2) N-Acetylcysteine Improves Transplant-Free Survival; Gastroenterology;2009:137(3):856-64
Acetaminophen Toxicity

- Most ingestions leading to ALF exceeds 10 g/day
- Severe toxicity reported with 3-4 g/day in alcoholics or malnourished patients
- Low or absent level does not rule it out
- Very high AST & ALT (>3500) is highly suggestive
- Early rise of serum AFP indicates good prognosis
- Fall of serum PO4 indicates improving
Drug-induced ALF

Recipients who underwent liver transplantation for drug-induced acute liver failure from 1987 through 2006 were analyzed. The leading drugs cause acute liver failure were acetaminophen, antituberculosis drugs, antiepileptics and antibiotics.

Children who had acute liver failure due to antiepileptics had a substantially higher risk of death after liver transplantation in comparison with other drugs. (1)

DRUG induced ALF

- **DIALF** due to antiepileptics (at age < 18) and elevated serum creatinine were independent pretransplant predictors of poor survival after LT for **DIALF**

- (1) Doctors Evaluate Predictors of Poor Survival after Liver Transplantation; Liver Transplantation; 2009:15(7):719-29
NAC in Non-acetaminophen ALF

- 173 pts from ALF study randomized to receive 72 hrs of IV NAC
- Primary endpoint: overall survival (OS)
- Secondary endpoint: spontaneous (transplant free) survival (SS)
- No difference in OS (57/81 vs 61/92)
- No difference in SS (32/81 vs 25/92)
- No difference in SS among HE grade III-IV (2/23 vs 8/36)
- No difference in OS among grade III-IV (p=0.09)
- SS significantly better with NAC among HE I-II (30/58 vs 17/56)

Abstract # 79, AASLD Annual Meeting, November 2007
Wilson’s Disease

- High bilirubin
- Low ALP
- Low uric acid
- Hemolytic anemia
- AST $> 4 \times$ ALT
- Kayser-Fleischer ring in 50% of pts
Screening for Wilson Disease in Acute Liver Failure: A Comparison of Currently Available Diagnostic Tests

Jessica D. Korman, Irene Volenberg, Jody Balko, Joe Webster, Frank V. Schiodt, Robert H. Squires, Jr., Robert J. Fontana, William M. Lee, Michael L. Schilsky and the Pediatric and Adult Acute Liver Failure Study Groups

- AST:ALT > 2.2 (94% sensitivity & 86% specificity)
- AP:TB < 4 (94% sensitivity & 96% specificity)
- Both criteria together (100% sensitive and specific)
Autoimmune Hepatitis

- Antibodies may be absent
- Liver biopsy may help with diagnosis
- High levels of IgG suggests the AIH
- Steroid may help (40-60 mg/d), or may not

*Liver Transplantation 2007;13:996-1003*
Herpes Simplex-Induced Fulminant Hepatitis In Adults
A Call For Empiric Therapy

DAVID J. PETERS, DO, WALLACE H. GREENE, PhD, FRANCESCA RUGGIERO, MD, and THOMAS J. McGARRITY, MD

- Anicteric hepatitis
- AST > ALT
- Rash in 50% of patients
- DX: HSV IgM, HSV DNA PCR, Biopsy
- Highly lethal if untreated

Dig Dis Sci 2000;45:2399-2404
The most recent issue of *Hepatology* reports that mortality of pregnant patients with acute liver failure is similar to that of nonpregnant women and girls, and men and boys, and is independent of the cause or trimester.\(^{(1)}\)

\(^{(1)}\) Pregnancy as a Prognostic Indicator in Acute Liver Failure; *Hepatology*; 2008:48(5):1577-85
OBESITY

- Obesity does not appear to be more prevalent in acute liver failure.
- However, obese and severely obese patients had significantly poorer outcomes when they developed ALF, even when controlling for age, gender, race, comorbid illness, MELD score, etiology of ALF.

RUTHERFORD, TIM DAVERN, J. EILEEN HAY, and et al; Influence of High Body Mass Index on Outcome in Acute Liver Failure; CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2006;4:1544–1549
The decision to list emergently an ALF patient for OLT is rarely easy.

The inherent risks associated with delaying listing for OLT must be balanced against the potential for spontaneous recovery with medical therapy alone.

Accurate prognostication in ALF is therefore vital, and many proposed mathematical, serological, radiological and histological variables have been proposed.
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Liver transplantation

- OLT has been recommended for the treatment of ALF since 1983.

- Emergency OLT for ALF now accounts for 5–12% of all liver transplantation activity & is the only treatment to alter substantially the mortality resulting from the condition.
Patient survival following OLT for ALF is generally poorer than that in those transplanted for chronic liver failure, but is of the order of 65–80% 1 year survival. (1)

(1) D. G. N. CRAIG, A. LEE, P. C. HAYES & K. J. SIMPSON, Review article: the current management of acute liver failure; Aliment Pharmacol Ther 31, 345–358
Liver transplantation

- Alternatives to standard OLT are being refined, including:

  1- living donor grafts
  2- auxiliary liver transplantation (where part of the native liver is left in situ after partial liver transplantation)

(4) D. G. N. CRAIG, A. LEE, P. C. HAYES & K. J. SIMPSON, Review article: the current management of acute liver failure; Aliment Pharmacol Ther 31, 345–358
Transplantation

- Overall outcome not as good as chronic liver failure
- Patient receives allocation Status 1A
  - FHF (HE within 8 wks of the onset of the liver disease) and vent dependent or on dialysis or INR>2 or
  - Primary non-function of LT within 7 days or
  - Hepatic artery thrombosis within 7 days of LT or
  - Acute decompensated Wilson’s disease or
- Re-listing every 7 days
- Role of living donor transplant is controversial (contraindicated in NY state for adult patients)

*United Network for Organ Sharing (UNOS) web site*
Auxiliary Transplantation
Liver transplantation

- In the largest U.S. study, only 29% of patients received a liver graft, while 10% of the overall group (1/4 of patients listed for transplantation) died on the waiting list. (1)

  median waiting time to transplantation is 3 days

Liver transplantation

- Other series have reported death rates of those listed for transplant as high as 40%, despite the fact that ALF remains the one condition for which the most urgent (UNOS status 1) listing is reserved.\(^{(2)}\)

<table>
<thead>
<tr>
<th>Center</th>
<th>Number of patients</th>
<th>Study period</th>
<th>Early patient survival(%)*</th>
<th>One year patient survival(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pittsburgh</td>
<td>42</td>
<td>1980-1987</td>
<td>74</td>
<td>59</td>
</tr>
<tr>
<td>Chicago</td>
<td>19</td>
<td>1984-1988</td>
<td>74</td>
<td>58</td>
</tr>
<tr>
<td>Michigan</td>
<td>19</td>
<td>1985-1990</td>
<td>NR</td>
<td>68</td>
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<tr>
<td>Nebraska</td>
<td>30</td>
<td>1986-1991</td>
<td>75</td>
<td>42</td>
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<tr>
<td>San Francisco</td>
<td>35</td>
<td>1988-1992</td>
<td>94</td>
<td>92</td>
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<tr>
<td>Philadelphia</td>
<td>18</td>
<td>1985-1990</td>
<td>65</td>
<td>95</td>
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<tr>
<td>USA (Multicenter)</td>
<td>121</td>
<td>1994-1996</td>
<td>NR</td>
<td>76</td>
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<tr>
<td>USA (Multicenter)</td>
<td>89</td>
<td>1998-2001</td>
<td>84</td>
<td>NR</td>
</tr>
<tr>
<td>Overall</td>
<td>373</td>
<td>1980-2001</td>
<td>80</td>
<td>70</td>
</tr>
</tbody>
</table>

(187/233) (198/284)

*early patient survival reflects discharge from the hospital following transplantation
NR= not reported
Liver Support Systems

- In a randomized, controlled trial in China, the Extracorporeal Liver Assist Device (ELAD) significantly increased transplant-free survival in 69 patients with chronic hepatitis B, compared with a standard of care control therapy.
ELAD

- The ELAD passes a patient’s plasma through cartridges lined with the living hepatocytes; the cells remove accumulated toxins while providing the metabolites normally produced by a healthy liver.

- At least 72 hours of continual treatment are necessary to detoxify the blood and restore liver metabolite levels sufficiently for the patient to recover.
At Beijing Youan Hospital, the ELAD passes the patient’s plasma through cartridges lined with living human hepatocytes.
Liver Support Systems

- Survival for patients with 24-48 hours on ELAD was about 50%, but increased to almost 90% as ELAD time increased to 72 hours. After 72 hours, survival began to decline slightly.

- Every extracorporeal device uses up platelets, but that is easily managed, with transfusions. (1)

(1) MICHELE G. SULLIVAN; Liver Assist Device: Chinese Data Exciting but Preliminary GI & HEPATOLOGY NEWS, MARCH 2008