急性肝衰竭

國際診療現況

李宣書
台灣大學生物科技研究所/臺大醫院內科部

Outline

- Definition of acute liver failure (ALF)
- Etiology of ALF
- Treatment of ALF
- Determinants of ALF outcome and models for selection of liver transplantation

What is ALF

- “A complex multi-systemic illness that evolves after a catastrophic insult to the liver manifesting in development of a coagulopathy and encephalopathy within a short period of time.”

- Synonymous with fulminant hepatitis, fulminant hepatic failure, fulminant liver failure

1) O'Grady J G et al; Postgrad Med J 2005; 81: 148~154

Lack of Universal Definition

- *Trey C et al*[1]: Fulminant hepatic failure (FHF) as "onset of altered mental status within 8 weeks of initial symptoms in an otherwise healthy individual with no previous history of liver disease."
- *Bernuau J et al*[2]: FHF reserved for encephalopathy within 2 weeks of onset of jaundice, subfulminant FH between 2 weeks to 3 months
- *O'Grady et al*[3]: based on jaundice-to-encephalopathy interval, hyperacute: within one week, acute: between 8~28 days, and subacute: between 29 days to 12 weeks

1) N Eng J Med 1968;6:648~651
2) Hepatology 1986; 6:648~651
3) Lancet 1993; 342: 273~275

定義者	定義與分類
Trey (1970)	Fulminant hepatic failure = 以往無肝臟疾患者因肝臟受損，於「肝病症狀」發生後8個星期內引起肝性腦病變者，此爲一可完全康復之情況。
Williams (1986)	Late-onset liver failure = 如上所述，但是於「肝病症狀」發生後8~26星期內引起肝性腦病變者。
Bernuau (1986)	Fulminant liver failure = 出現「黃疸」後2星期內發生腦病變者。 Subfulminant liver failure = 出現「黃疸」後2~12星期內發生腦病變者。
Williams (1993)	Hyperacute liver failure = 出現「黃疸」後7天內發生腦病變者。 Acute liver failure = 出現「黃疸」後8~28天內發生腦病變者。 Subacute liver failure = 出現「黃疸」後29天至12星期內發生腦病變者。 (但是以上三種又統稱爲acute liver failure)

內科學第五版，橘井文化， 2007

AASLD Recommendation

- Evidence of coagulation abnormality, usually an INR >1.5 and any degree of mental alteration in a patient without preexisting cirrhosis and with an illness of < 26 weeks duration
- Wilson's disease, vertically-acquired HBV, autoimmune hepatitis may be included.
- ***Acute liver failure***, a better overall term, encompass all durations up to 26 weeks.

Polson J et al: Hepatology 2005; 41: 1179~1197

表 4：肝性腦病變之臨床分期

臨床分期	精神狀態	EEG 變化	Flapping tremor
I	輕微錯亂，稍煩躁，性格出現變化注意力不集中，心智功能測試反應變慢，睡眠型態改變	−	+／−
II	嗜睡，心智功能測試結果大多不對，性格完全不一樣，不合宜之行為出現，對時間之概念不正確	+	+
III	幾乎一直在睡，但可叫醒之，無法接受心智功能測試，明顯錯亂，對時間及地方之概念不正確	+	+
IV	昏迷	+	−

EEG：Electroencephalogram

內科學第五版，橘井文化， 2007

Outline

- Definition of acute liver failure (ALF)
- Etiology of ALF
- Treatment of ALF
- Determinants of ALF outcome and models for selection of liver transplantation

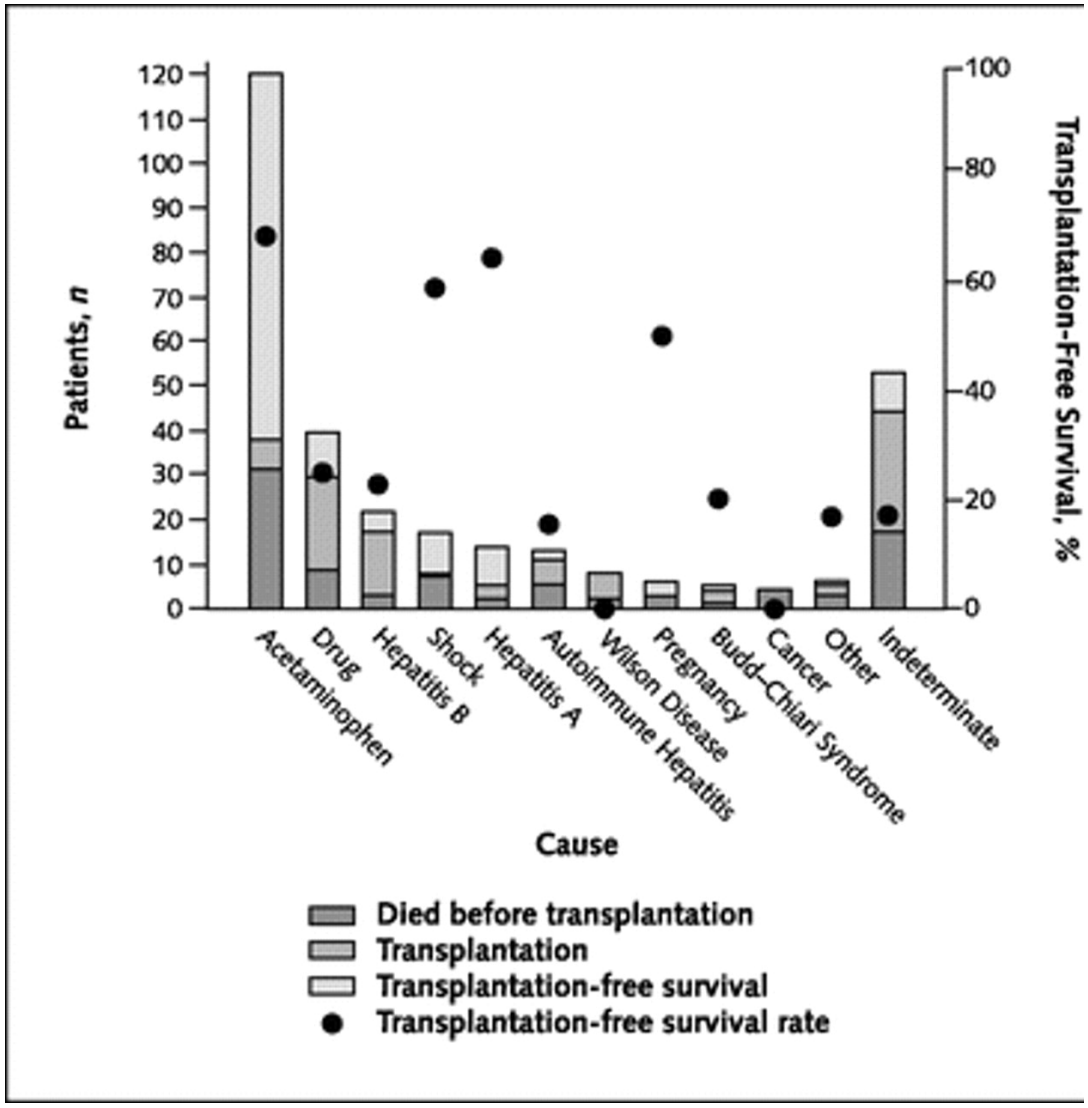
UK & US: Acetaminophen

Table 1 Selected Reports of Worldwide Etiology of Acute Liver Failure

			Etiology			
			Drug-Induced			
Study	Reference	n	Acetaminophen	Nonacetaminophen	Viral	Seronegative
UK 1973–1990 King's, London	O'Grady,[38] Sallie et al[39]	943	53%	7%	19%	17%
UK 1991–1997 King's, London	Ellis et al[7]	999	70%	5%	5%	7%
India 1991–1996	Dhiman et al[6]	204	0%	7%	91%	2%
USA 1994–1996	Schiodt et al[101]	295	20%	12%	17%	15%
USA 1998–2001	Ostapowicz et al[8]	308	39%	13%	12%	17%

Bernal W. Semin Liver Dis 2003 (23)3: 227-237.

US: Acetaminophen



- Acetaminophen 39%
- Other drug 13%
- HBV+HAV 12%
- Indeterminate 17%

Ostapowicz, G. et. al. Ann Intern Med 2002;137:947-954

East: Viral Hepatitis

Table 1 Etiology of Acute Liver Failure in the Far East

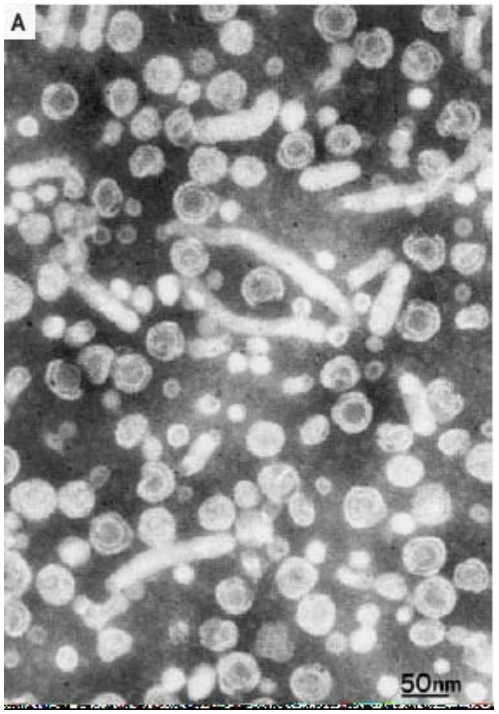
Etiology	Hong Kong	Taiwan	Japan	India
Hepatitis B	79%	63%	22%	31%
Hepatitis C	NA	NA	NA	NA
Hepatitis A	NA	NA	12%	2%
Hepatitis E	NA	NA	NA	38%
Seronegative hepatitis	NA	NA	NA	24%
Drug reactions	NA	NA	14%	5%
Unknown etiology	NA	NA	62%	NA

NA, not available

Cheng V C et al; Semin Liver Dis 2003 (23)3: 217-26

Taiwan: Probably Hepatitis B

- 90% of viral hepatitis related fulminant hepatitis were HBs Ag (+)[1]
- 93.8% liver transplantation for ALF were HBV related in NTUH[2]
- 81.25% fulminant and subfulminant hepatitis were HBV associated: coinfection with HDV, HCV or reactivation of CH-B[3]



1) *Chu CM et al; Infection 1990; 18:200-3*
2) *Wu YM et al; Trans Proc 2004; 36:2226~7*
3) *Wu JC et al; Hepatology 1994;19: 836~40*

Outline

- Definition of acute liver failure (ALF)
- Etiology of ALF
- Treatment of ALF
- Determinants of ALF outcome and models for selection of liver transplantation

Treatment of ALF

- Intensive care, monitoring
- Specific treatment
  - Acetaminophen: N-acetylcysteine
  - HBV: nucleotide analogues
  - Autoimmune hepatitis: corticosteroid
  - Pregnancy-associated: delivery
- Dialysis
  - Charcoal hemoperfusion, exchange plasmapheresis, MARS
- Liver transplantation

N-acetylcysteine in non-acetaminophen-induced ALF

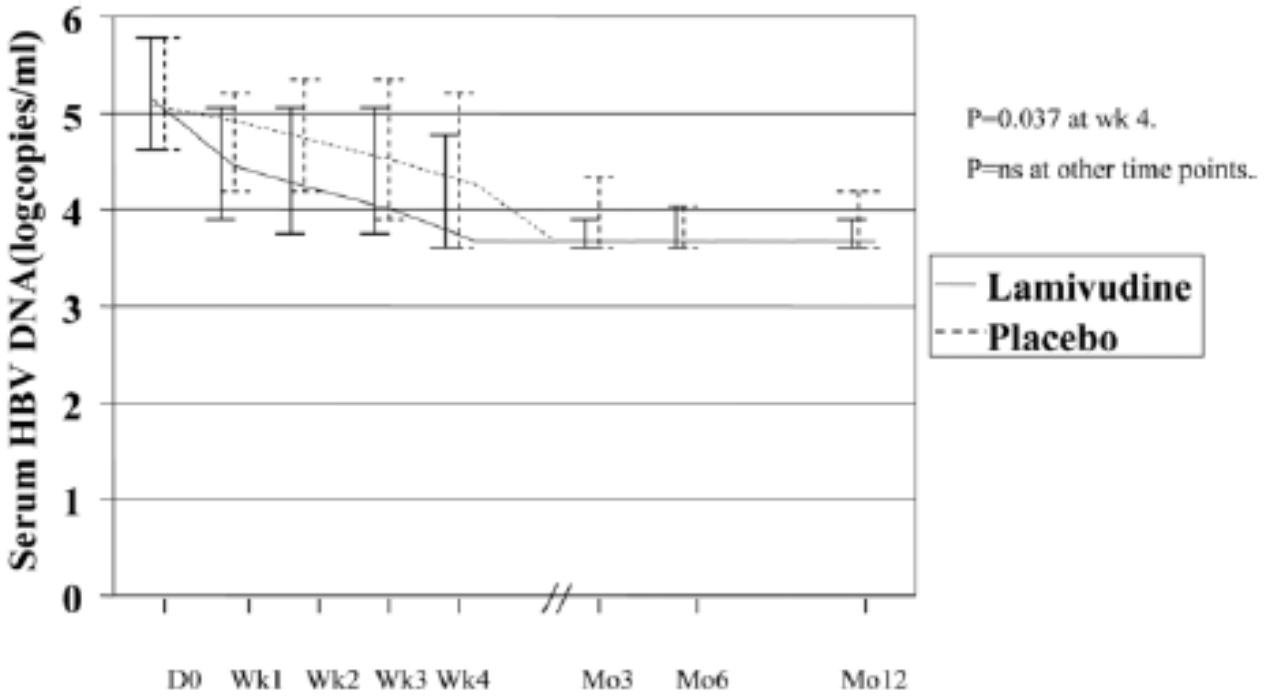
Table 1 | NAC treatment for acute liver failure not due to paracetamol overdose[18]

Outcome	Grade 1 or 2 hepatic encephalopathy		All grades of hepatic encephalopathy		Overall *P* value
	Placebo ($n=56$)	NAC ($n=58$)	Placebo ($n=92$)	NAC ($n=81$)	
Survival at 21 days (%)	75	79	66	70	0.283
Survival at 1 year (%)	61	72	57	63	0.195
Transplant-free survival at 1 year (%)	18	45	18	35	0.008
Proportion of patients transplanted at 1 year (%)	52	28	48	32	0.035

Abbreviation: NAC, *N*-acetylcysteine.

Lee WM et al; Gastroenterology, in press

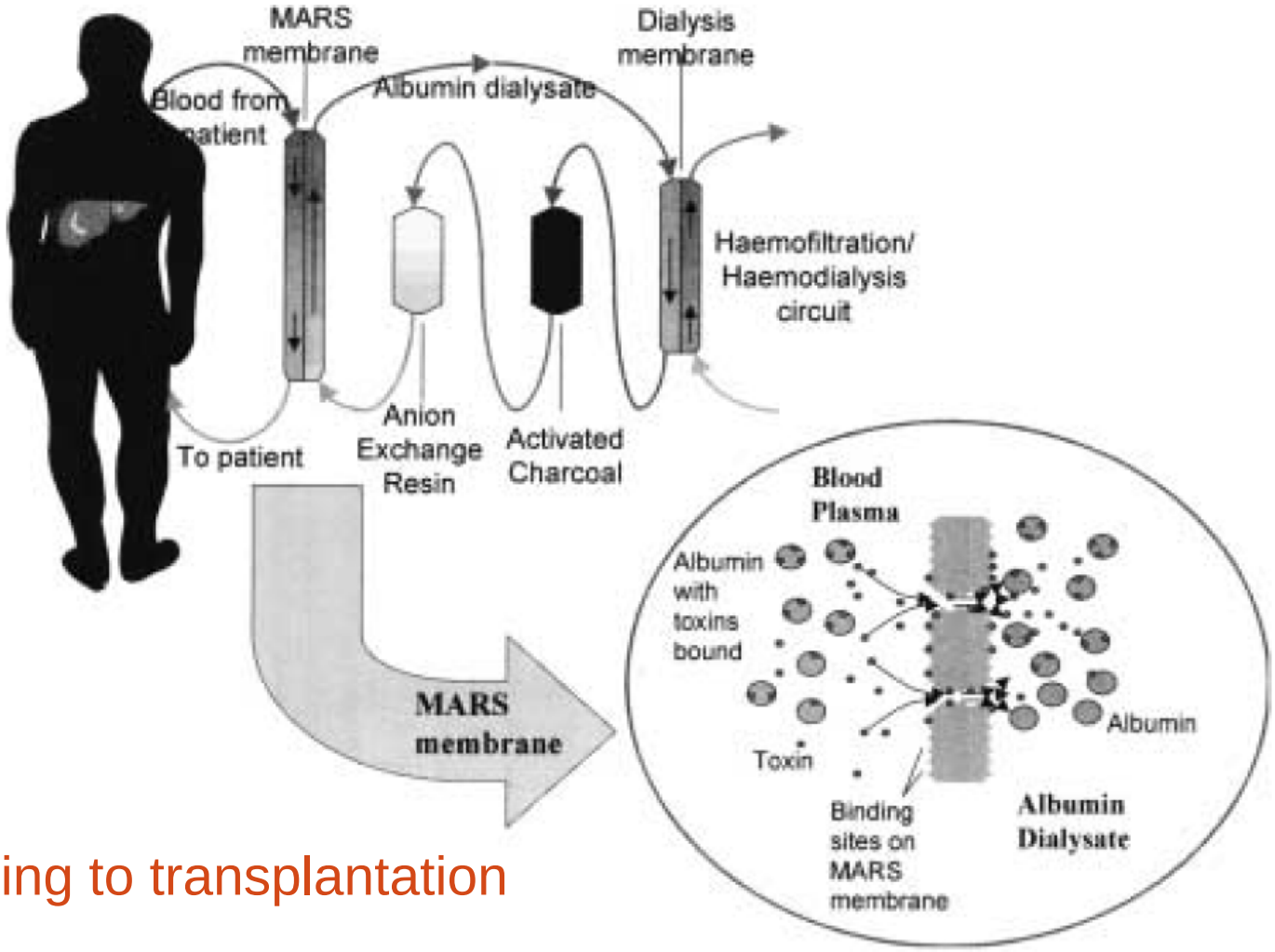
Lamivudine in acute hepatitis B



In conclusion, although lamivudine caused a greater decrease in HBV DNA levels in patients with acute hepatitis B, it did not produce significant biochemical and clinical improvement compared to that in patients who received the placebo.

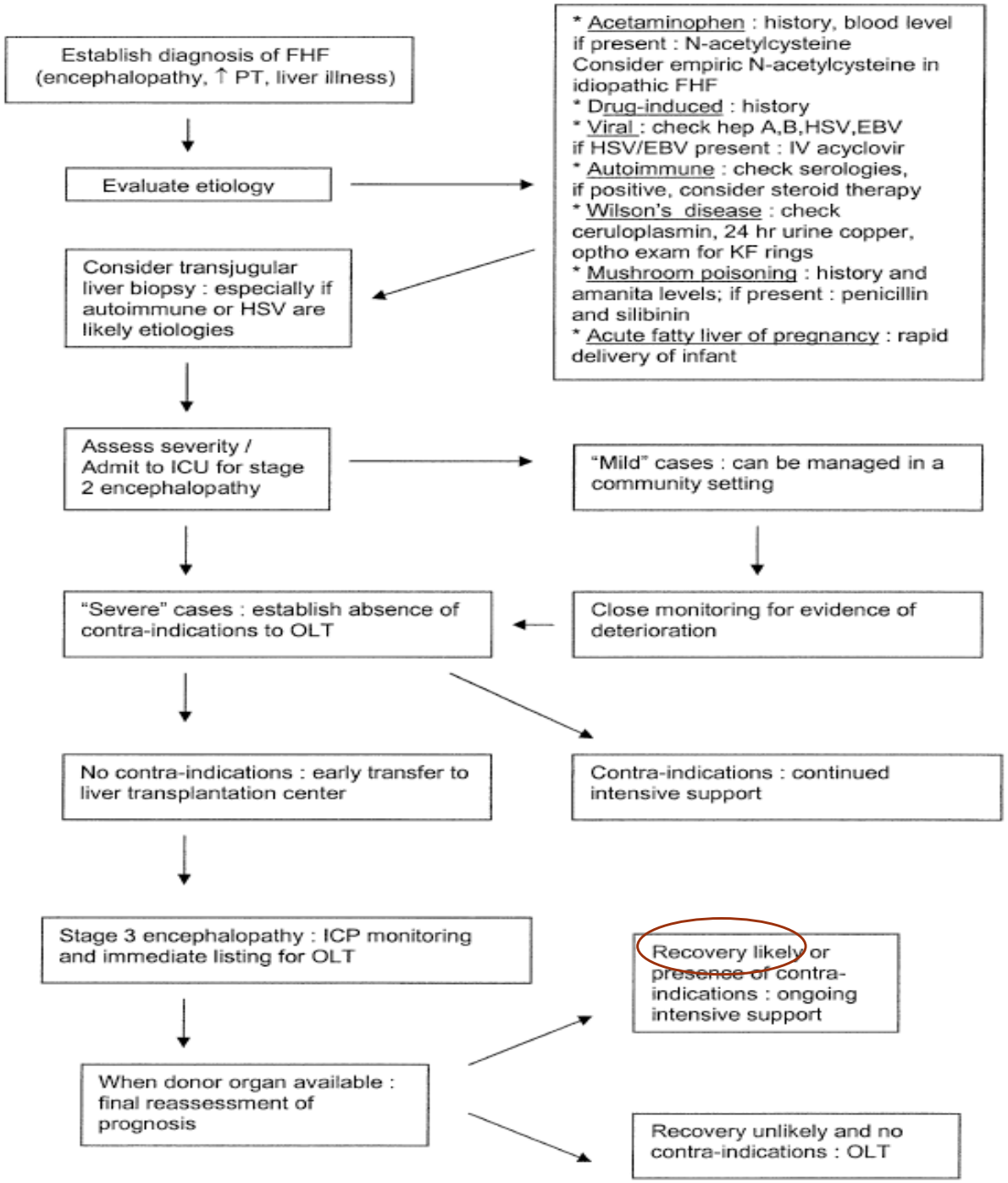
Kumar M et al; Hepatology 2007;45:97-101

Molecular adsorbent recirculating system (MARS) in ALF



Bridging to transplantation

Mitzner SR et al; ASAIO J 2009, 498-502



Gastroenterol Clin North Am 32 (2003) 1195–1211

Outline

- Definition of acute liver failure (ALF)
- Etiology of ALF
- Treatment of ALF
- Determinants of ALF outcome and models for selection of liver transplantation

Table 1. Variables That Correlate With Outcome in Patients With Fulminant Hepatic Failure

Variable	Outcome
Clinical	Age
	Degree of encephalopathy
	Rate of development of encephalopathy
	Etiology
	Intracerebral hypertension
Serological	Bilirubin
	Creatinine
	Clotting variables, such as INR, Factor V[19]
	Lactate[15]
	Phosphate[11]
	Ketone Body ratio[18]
	Alfa-fetoprotein[12]
	Gc protein[16]
	Valine[8]
	pH
	Pre-albumin
	Cholinesterase
	MELD score[10]
Functional	Galactose elimination capacity[15]
Physiological	APACHE II[9]
	Hepatic artery resistance index changes[13]
Histological	Degree of liver cell necrosis[14]
Morphological	Liver volume[17]

Models to select patients for transplantation

- King’s College Criteria
- Clichy Criteria
- Edinburgh’s biochemistry model
- MELD Score

King's College Hospital Criteria

King's College criteria for liver transplantation

Acetaminophen	*Non-acetaminophen*
pH < 7.3 (irrespective of grade of encephalopathy)	PT > 100 s (INR > 6.5) (irrespective of grade of encephalopathy)
or all three of the following	*or any three of the following*
Grade III–IV encephalopathy	Age < 10 or > 40 y
PT > 100 s (INR > 6.5)	Etiology: non-A, non-B hepatitis; halothane; idiosyncratic drug reaction; Wilson's disease
Serum creatinine > 300 µmol/L (3.4 mg/dL)	Period of jaundice to encephalopathy > 7 d
	PT > 50 s (INR > 3.5)
	Serum bilirubin > 300 µmol/L (17.5 mg/dL)

O' Grady JG et al; Gastroenterology 1989;97:439- 455.

Validation of KCH Criteria (I)

TABLE 3

Reappraisal of King's College Hospital criteria in fulminant hepatic failure patients seen at Birmingham during 1990–94. Separate analysis has been done for values noted on arrival at the Liver Unit, Birmingham, and the peak values noted during the course of the illness (values are expressed as percentages)

	Values on admission to Queen Elizabeth Hospital			Peak values during admission to Queen Elizabeth Hospital		
	Positive predictive value	Negative predictive value	Predictive accuracy	Positive predictive value	Negative predictive value	Predictive accuracy
1. KCH criteria for acetaminophen-induced fulminant hepatic failure						
(a) pH <7.25	83	59	64	75	60	66
(b) pH <7.30	86	62	68	77	64	70
(c) Prothrombin time >200 s, creatinine >300 µmol/l and encephalopathy grade 3 or more	83	64	65	79	72	73
(d) Either (b) or (c)	88	65	71	73	71	72
2. KCH criteria for non-acetaminophen-induced fulminant hepatic failure						
(a) Prothrombin time >100 s	100	32	38	100	37	52
(b) Any three of following: age <10 or >40 years, unfavorable etiology, jaundice >7 days before onset of encephalopathy, prothrombin time >50 s and bilirubin >300 µmol/l	77	44	64	65	17	52
(c) Either (a) or (b)	79	50	68	68	25	61

Anand et al; J Hepatology 1997;26: 62~68

Validation of KCH Criteria (II)

Table 4. Diagnostic Accuracy of King's College Hospital Criteria

	Survival*						
	Criteria+	Criteria–	Sensitivity	Specificity	PPV	NPV	PA
Acetaminophen							
pH <7.30							
KCH	1/22	—	0.49	0.99	0.95	—	0.81
Pittsburgh†	4/13	4/5	0.90	0.50	0.69	0.80	0.72
Pittsburgh (+OLT)‡	4/16	4/10	0.67	0.50	0.75	0.40	0.62
INR >6.5, serum creatinine >3.4 mg/dL, grade III-IV encephalopathy							
KCH	5/15	—	0.45	0.94	0.67	—	0.83
Pittsburgh	0/8	11/14	0.73	1	1	0.79	0.86
Pittsburgh (+OLT)	0/12	11/20	0.57	1	1	0.55	0.72
Nonacetaminophen							
INR >6.5							
KCH	0/15	—	0.34	1	1	—	0.46
Pittsburgh	1/42	13/26	0.76	0.93	0.98	0.50	0.79
Pittsburgh (+OLT)	1/82	13/58	0.64	0.93	0.99	0.22	0.67
Any 3 of 5 variables§							
KCH	1/28	—	0.93	0.90	0.96	—	0.92
Pittsburgh	4/44	10/24	0.74	0.71	0.91	0.42	0.74
Pittsburgh (+OLT)	4/94	10/48	0.70	0.71	0.96	0.21	0.70

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; PA, predictive accuracy; KCH, King's College Hospital Study.
*Survival according to fulfillment (+) or lack of fulfillment (–) of King's College Hospital's criteria (number survived/group total).

Shakil et al; Liver Transpl 2000;6:163–9

Clichy Criteria

- Age, presence of HBsAg, serum AFP and serum factor V were independent prognostic factors.
- Factor V < 20% in pt < 30 y/r old
  Factor V < 30% in pt 30 y/r or older
- Single etiology and measurement of factor V
- Weaker performance than KCH criteria in validation study

Bernuau et al; Hepatology 1986; 6: 648~651
Bernuau et al; Hepatology 1991; 14: 49A

Edinburgh Biochemistry Criteria

- 0.5(albumin [g/L]) - 2*(lactate [mmol/L]) - 36*(valine [mmol/L]) - 38*(pyruvate[mmol/L
- Established on admission regardless of etiology and patients' demographics

TABLE 6. Comparison between the two sets of criteria

Biochemical criteria	Poor prognosis	Good prognosis
Biochemical criteria +ve	32	3
Biochemical criteria −ve	3	21
Positive predictive value 91%, negative predictive value 86%, sensitivity 94%, specificity 86%		
KCH criteria on admission	Poor prognosis	Good prognosis
KCH criteria +ve	12	2
KCH criteria −ve	21	24
Positive predictive value 83%, negative predictive value 43%, sensitivity 45%, specificity 88%		
KCH criteria overall	Poor prognosis	Good prognosis
KCH criteria +ve	29	4
KCH criteria −ve	6	20
Positive predictive value 84%, negative predictive value 77%, specificity 79%, sensitivity 81%		

Biochemical criteria on admission had better positive and negative predictive values, sensitivity, and specificity than the KCH criteria on admission and overall in our study population.

KCH, King's College Hospital; +ve, positive; −ve, negative.

Dabos et al; Transplantation 2004; 77:200~205

MELD Score

- 9.57*$\log_e$(creatinine mg/dL) + 3.78*$\log_e$ (bilirubin mg/dL) + 11.20*$\log_e$ INR + 6.43 (constant for liver disease etiology)
- Originally developed to predict TIPS outcome
- Currently used for allocation of liver graft to adult cirrhotic patients in US.

	A (n = 330)		NA (N = 412)	
	PPV	NPV	PPV	NPV
MELD >30	52	82	81	41
INR> 3	48	72	82	35
Bil> 17.5	60	64	85	46
INR+Bil >20.5	64	63	90	47

Malinchoc M et al; Hepatology 2000; 8: 851~858

Problems left

- What are the epidemiologic features of ALF in Taiwan?
- From hepatitis to live failure: who will or will not progress? what treatments make difference?
- How well current prognostic models work?
- Any undiscovered prognostic factors?

To Transplant or Not

Selection of patients and timing of transplantation… literally life and death decisions…usually with inadequate information and too little time.

Thank you for attention!