Liver Failure Syndromes

Treatment and management

Potential Categorization of liver dysfunction in critical care /MOF

- Primary liver Injury Acute
- Acute liver Injury
- Acute Liver Failure
- **Chronic liver failure**
- **Decompensated CLD**
- Acute on CLD

- Surgical
- Hepatectomy
- Trauma
- Liver Bx / ERCP

- Secondary liver Injury
- Sepsis / inflammation
- Systemic disease
- Drugs ; cholestasis
- Other.....



Acute Liver Failure

Primary liver injury

Coagulaopthy

Encephalopathy

No preexisting liver disease

Hyperacute < 7 days Acute 1 -4 weeks Subacute 4-12 weeks

Cirrhosis





Principle Causes of Acute Liver Failure

Cause Agent responsible

- Viral hepatitis Hepatitis A, B, D E, CMV, HSV, Seronegative indeterminate hepatitis (14 25% of cases)
 Reactivation of HBV Chemotherapy , steroids : antiviral Rx
 Drug related Paracetamol, Anti tuberculous drugs, lipid
- Recreational drugs, Idiosyncratic reactions anticonvulsants, NSAI, HARRT etc, etc
- Toxins Amanita phalloides
- Vascular events Hypoxic Hepatitis, VOD, Budd-Chiari Hyperthermia induced ALF (NMDA, excercise)
- Pregnancy related Liver rupture, HELP, fatty liver
- Other Lymphoma, carcinoma : imaging , LDH, AlKP04 Wilson disease : low AlkP04, haemolysis, spleen

Weils / leptospirosis – not really ALF

Management

- Diagnosis
 - Imaging
 - Role of biopsy
- Supportive therapy to allow scenario for liver regeneration or stability for transplantation
 - CVS
 - Respiratory
 - CNS
 - Renal
 - Feeding
 - Sepsis
 - Coagulation monitor do not Rx
 - G-I : consider pancreatitis

Consider Tf / discuss with tertiary centre



Treatment / prevention

- Antiviral therapy in hepatitis B, CMV, HSV
 - N-acetyl cysteine Harrison et al keays et al 1992 BMJ, Lee W
 Gastroenterology 2009, Dig Dis Sci (2013) 58:1397–1402, Liver Int. 2013: 33: 1324– 1331 (IL-17)
- Removal of potential toxic drugs
- TIPS shunt in acute Budd Chiari
- Delivery in pregnancy related pre-eclampsia





Pregnancy related liver disease





Diagnosis

Be open to rare diagnoses

Imaging and blood tests

HSV and pregnancy

Transfer issues

- 1. Early transfer to a Tp centre
- 2. Elective ventilation if GCS

changing

- 3. Observe pupils
- 4. Fluids
- 5. Noradrenaline
- 6. Mannitol for pupil abnormalities

Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography

Journal of Hepatology **2012** vol. 56 | 129–136

Eastura	Normal Danca	Entire Crown	Chantonaalia Curvivara	Death ar OLT
Fibrinogen (mg/dl)	200-450	195 ± 84	223 ± 55	154 ± 102**
		34+17	30+13	4 0 + 1 9*
MELD scoro		313+86	0.0 ± 1.0	36.2 + 8.2***
Maximum Amplitude (mm)	50.6-69.4	55.0 ± 10.9	55.0 ± 11.2	D.6
Lysis 30 (%)	0.0-7.5	0.0 [0.0-2.1]	0.0 [0.0-1.8]	2.1]
80 -				
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30				
0 1	2 3	4		

SIRS (N)



abnormal coagulation decreased clotting factors except FVIII.

Decreased anticoagulant factors and thrombin generation.

Intact haemostatic capacity when TG was measured in the presence of thrombomodulin .

Role of Procoagulant Microparticles in Mediating Complications and Outcome of Acute Liver Injury/Acute Liver Failure

R. Todd Stravitz,

HEPATOLOGY 2013;58:304-313)



Fig. 5. Prevalence of MP phenotypes in plasma of patients with ALI/ALF by flow cytometry.

Lung Injury and Its Prognostic Significance in Acute Liver Failure CCM March 2014 • Volume 42 • Number 3

Georg Auzinger

- 148 patients with ALF
- 21% incidence of ALI/ARDS
- No effect on mortality
- ITU LoS longer 9 vs 19 days (p<0.01)
- EVLWI had a sensitivity of 65% &

specificity of 77% in prediction of ALI/ARDS

Simplified Acute Physiology Score	52 (12-97)	52 (23–92)	0.780
Sequential Organ Failure Assessment	15 (6-21)	16 (8–20)	0.886
Liver intensive therapy unit stay (d)	16 (1–59)	19 (2-140)	0.086
Ventilator days	10 (-50)	15 (2-41)	0.020
Outcome (dead/transplanted:spontaneous survival)	69:48	17:14	0.883

CVS management

- Volume
- Avoid right sided overload
- Cardiac injury / disease
- Vasopressor
 - Norepinephrine / vasopressin
- Role of hydrocortisone
- Consider HH

Troponin Often elevated –0.1 up to 24 ng/L OR death 3.8 for > 0.1 Parekh Hepatology 2007 45:1489

> Audimooolam et al. Critical Care 2012, 16:R228 Fin larsen et al Harry et al Hepatology 2002





Hypoxic hepatitis

- Global haemdynamics vs splannchnic haemodynamics
- Inadequate hepatic arterial inflow / oxygenation
- Portal venous inflow issues
- Hepatic venous outflow
 - R heart issues
 - veno-occlusive disease
 - sickle hepatopathy, malaria
- Microcirculatory abnormalities
- Intra-abdominal hypertension
- Infiltration (lymphoma, adeno, leukaemia)
 - 1. Henrion et al Medicine 82 : 6 ; 2003, Liver
 - 2. Mayo Clin Proc 2006 81(9) :1232



Prevelance 1.5 -12%

Author date (ref.)	Henrion 2003 (2)	Birrer 2007 (3)	Fuhrmann 2009 (5)	Chang¶ 2008 (20)	Raurich § 2010 (7)
No. of cases	142	322	118	75	182
S-AT x ULN *	20	10	20	75	20
Heart failure	100 (70%)	201 (62%) †	61 (52%) ‡	47%	71 (39%)**
Respiratory failure	19 (13%)	45 (14%) †	23 (20%) ‡	11%	<7%
Septic shock	19 (13%)	52 (16%) †	37 (32%) ‡	32%	60 (32%)

Table 3. Clinical conditions underlying hypoxic hepatitis in the five largest and most recent series

Table 4. Hemodynamic assessment in hypoxic hepatitis caused bycardiac failure (results expressed as medians)

Table 5. Hemodynamic assessment in hypoxic hepatitis becauseof respiratory failure (results expressed as medians)

Author (ref.)	J. Henrion (2)	B. Birrer (3)	Normal values (36)
No. of cases CVP (cm H_2O) CI (L/min.m ²) DO ₂ (ml/min.m ²) PaO ₂ (mmHg) HBE (ml/min.m ²)	73 21 1.97 (<i>n</i> = 34) 350 (<i>n</i> = 34) 64 795 (<i>n</i> = 18)	198 20 1.91 325 84 778	- 1-9 2.8-3.6 520-720 80-98 2100*

Author (ref.)	J. Henrion (2)	B. Birrer (3)	Normal values (36)
No. of cases	19	51	_
CVP (cm H_2O)	17.5	16	1–9
CI (L/min.m ²)	3.8 (<i>n</i> = 8)	3.9	2.8–3.6
DO_2 (ml/min.m ²)	394 (n = 8)	382	520–720
PaO ₂ (mmHg)	34	32	80–98
HBF (ml/min.m ²)	1283 (<i>n</i> = 4)	1304	2100*

DO₂, oxygen delivery; CI, cardiac index; CVP, central venous pressure;

Hypoxic hepatitis

Jean Henrion

Hepatopulmonary Syndrome in Patients With Hypoxic Hepatitis

GASTROENTEROLOGY 2006;131:69-75

VALENTIN FUHRMANN,* CHRISTIAN MADL,* CHRISTIAN MUELLER,[†] ULRIKE HOL REINHARD KITZBERGER,* GEORG–CHRISTIAN FUNK,[§] and PETER SCHENK* *Intensive Care Unit 13H1; [†]Division of Gastroenterology and Hepatology; [§]Pulmonary Division, Department of Inte University Vienna, Vienna, Austria



Table 2. Arterial Blood Gas Analysis and Respiratory Parameters During CEE in Patients With HH
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	HPS-positive patients	HPS-negative patients	P value
Arterial blood gas analysis during CEE			
pH	$7.34 \pm .15$	$7.40 \pm .06$	NS
PaO ₂ , mm Hg	76 ± 11	92 ± 16	.001
PaCO ₂ , mm Hg	40 ± 15	40 ± 9	NS
AaDO ₂ , mm Hg	231 ± 126	204 ± 118	NS
Respiratory parameters in mechanically ventil	ated patients during CEE		
PEEP, mbar	7.5 ± 2.8	8.9 ± 4.1	NS
P max insp, <i>mba</i> r	22.2 ± 5.3	22.9 ± 6.2	NS
Tidal volume, <i>mL</i>	485 ± 90	531 ± 152	NS
Respiratory rate per minute	18 ± 5	16 ± 5	NS
PaO ₂ /FiO ₂	152 ± 61	203 ± 63	.034
AaDO ₂ , mm Hg	266 ± 102	215 ± 112	NS
AUC_{48hr} of PaO_2/FIO_2 , mm Hg \cdot h	7465 ± 2409 ^a	11,620 ± 4281 ^b	.009

: 01 May 2013

Andreas Drolz

Clinical impact of arterial ammonia levels in ICU patients with different liver diseases



Liver will recover

Acute kidney injury in patients admitted to a liver intensive therapy unit with ALF . *O'Riordan A* Nephrol Dial Transplant (2011) 26: 3501–3508

Period 2000-2007 : 302 ALF managed without OLT

21% did not develop AKI : all survived

239 with AKI of whom 164 survived

Lactate 2-7 INR 2-5

51% return of normal renal function eGFR > 60 discharge

7% required on going haemodialysis at time of discharge At 30 days post discharge of this group eGFR was 20 At 90 days none dialysis dependent and eGFR > 60 AKI does not impact on outcome om mutivariate analysis

Nephrol Dial Transplant. 2011 Nov;26(11): 3501-8.



Figure: Interorgan trafficking of ammonia in health and in cirrhosis In healthy individuals, liver removes ammonia by detoxification into urea. In patients with cirrhosis, metabolic capacity of liver is reduced, resulting in hyperammonaemia: muscle becomes important organ of ammonia detoxification into glutamine. Glutamine acts as temporary buffer that can both regenerate ammonia (enterocytes) and excrete ammonia (kidneys).

Indication for RRT Acidosis / Acidaemia Metabolic disarray : lactate Cl/Na control Ammonia clearance Hepatic encephalopathy

Liver International (2013)



Clinical Evidence of Intra-cranial Hypertension. All Severe HE. Split by admission INR



Grade III/IV coma Young people Haemodynamic instability Fever, SIRS, low Na Elevated NH4 (>150) Renal failure MCA dopplers

Bernal W Hepatology 2008

10% complication rate5% significant*Vaquero Liver Transplantation Dec 2005*





NH4 cut off 124 : pH, cerebral oedema + NH4 predict outcome *Bhatia V Gut 2005*

Bernal W Hepatology 2007



Figure 1 Arterial ammonia concentration (μ mol/L) in two groups of patients with fulminant hepatic failure (FHF): patients who did develop high ICP and patients who did not. For each group, baseline values and values taken later during FHF are given. **P*<0.05 versus baseline values in both groups.



ICP 45 (25-49) 16 (13-17) * CBF 103 (25-134) 44 (24 -75) * CPP 45 (37-56) 70 (60-78) * CI 9.8 (7-13)5.1 (4.3-6.1) *

•Art NH4 343 (109 - 490) to 259 (100-453)* Restoration of autoregulation

Jalan et al Lancet 354: 9185 :1164 1999 Jalan et al Gastroenterology 2004;27:1338





Cerebral oedema is rare in acute-on-chronic liver failure patients presenting with high-grade hepatic encephalopathy. 2013

Deepak Joshi¹

Liver International ISSN 1478-3223



Table 1. Patient demographics and clinical parameters in whom neuroimaging was available

	ACLF (n = 81)	CLD (n = 92)	P-value
Age (years)	50 (24-71)	59 (30–74)	0.001
Sodium (mmol/L)	132 (118-154)	136 (120-146)	< 0.0001
Creatinine (mmo//L)	96 (44-800)	96 (41–655)	0.63
Albumin (g/L)	25 (12–54)	28 (16–54)	0.001
Bilirubin (µmo/L)	137 (85-804)	45 (6-575)	0.001
White cell count (×10 ⁹ /L)	8.9 (2.52–76)	6.4 (0.99–61)	0.03
INR	1.7 (1.5–5)	1.4 (0.9-4.5)	<0.0001
Platelets (×10 ⁹ /L)	66 (15–280)	88 (19-454)	0.02
Fibrinogen (g/L)	1.9 (0.4–6.0)	3.1 (1.3–6.4)	0.007
Arterial ammonia (µmol/L)	143 (40–305)	111 (28–315)	<0.0001
Child–Pugh	12 (5–13)	7 (5–13)	<0.0001
MELD	25 (8–40)	15 (6–34)	<0.0001
SOFA	11 (2–17)	4 (0–14)	<0.0001
SIRS score	2 (1–3)	1 (0–3)	<0.0001

	ACLF	CLD	P-value
Normal (n/%)	21/26	30/33	0.6
Increased cerebral atrophy for age (n/%)	21/26	30/33	0.6
Small vessel disease (n/%)	12/15	17/18	0.4
Intracerebral haemorrhage (n/%)	19/23	9/9	0.008
Cerebral oedema (n/%)	3/4	0/0	0.04
Other (n/%)	5/6	6/7	0.6

Table 2. Summary of CT findings between ACLF and CLD groups

72 ALF in grade III/IV coma underwent CT imaging : incidence of radiological cerebral oedema was 32%

Sodium Aetiology of Neurological NHa Age Sex cirrhosis Precipitant of ACLF abnormality Patient (years) (mmo/L) MELD SOFA HE grade (umo/L) 50 Female Cryptogenic Variceal bleed, Pupillary 134 38 8 4 289 1 culture-negative abnormality sepsis, TIPS 52 Culture negative sepsis Seizure 2 Female Alcohol 132 19 8 4 268 з Alcoholic hepatitis, sepsis 21 4 66 Female Alcohol Pupillary 137 9 238 abnormality

Table 3. Patient characteristics with ACLF and cerebral oedema on admission

- Agitation and airway management
 - Grade III : Intubate, ventilate and sedate with opiate and propofol
 - Control ventilation avoid alkalosis
- Position 10 to 20 degrees head up
- Insert reverse jugular line: JV sat 55 to 80%
- Control of glucose, K, pH, Na (145-150 mmol/L)
- Ammonia daily measurement: early CRRT; SIRS monitoring
- MAP > 60-65 : frequently not autoregulating need to measure ICP
- No CPP aim per se
- Treat "ICP" trigger > 25 or pupillary abnormalities
 - Hypertonic NaCI (30%) 20 ml Mannitol ; 150 ml 20% (osmolarity < 320)</p>
 - Indomethacin 0.5 mg/kg (25-50 mg) only if JV(r) high
- Hyperventilation only for ICP in association with high JV satn
- Temperature avoid fever : hypothermia should not be undertaken routinely

FULMAR (Saliba et al)

- Prospective, controlled, randomized parallel group trial
 - Total number of patients: 102 (ITT)
 - Main etiology of ALF due to Acetaminophen (38%)
 - SMT = 19, MARS=20
- Comparison of SMT versus SMT + MARS

Indication

- ALF, with and without indication for liver transplantation
- 68/102 patients transplanted
 - 41% of acetaminophen group
- Median delay listing to transplant was 16.2 hrs

Faouzi Saliba et al , AASLD 2008.

FULMAR Study

6 months patient survival / Etiology (ITT analysis)

Non Paracetamol

Survival curve for ITT patients with non paracetamol etiology

Paracetamol

© Cembro Renel Products US 071209 DG

Survival curve for ITT patients



..... Caliba at al 2000 Combro / locon ..*.*. **Г**.

Guidelines for referral

Paracetamol

Arterial pH < 7.30 or HC03 < 18 INR > 3.0 day 2 or > 4.0 thereafter oliguria and/or elevated creatinine altered conscious level hypoglycaemia

Children - coagulopathy

Budd Chiari

Pregnancy related

Non-Paracetamol

pH < 7.30 or or HC03 < 18 INR >1.8 oliguria/renal failure encephalopathy hypoglycaemia shrinking liver size < 1000 ml need OLT Na < 130 mmol/L Bilirubin > 300 µmol/l

ALF and Tx as an option: <u>if poor</u> prognostic criteria achieved

Yes

Drug related Acute Viral hepatitis Toxins Hepatic vein occlusion

Consider but very rarely required Pregnancy related Trauma

No

Ischemic hepatitis (HH) Systemic Disease HLH Metabolic disease Infiltrative Disease Lymphoma

Exceptions to rules

Acute Wilsons disease Children and young adults Intercurrent viral illness Stopped drugs Coagulopathy, haemolysis & low AIKP04

	Edinburgh 1992-2009	Birmingham 1992-2008	ALFSG 1998-2001
N with ALF	515	1237	308
Listed for LTX	154 (30%)	327 (26%)	135 (44%)
Actually transplanted	117(76%) (23% of all n)	263 (80%) (21% of all n)	89 (66%) (29% of all n)
Listed but no LTX Mortality in %	37 97%	64 77%	
No LTx	398 (77%)	974 (79%)	219 (71%)
Survived wout LTX	61%	74%	43%
Overall mortality of ALF		23-38% at 1 year	

Bretherick AD et al. Q J Med 2011; Marudanayagam R etal: HPB 2009, Ostapowicz G et al: Ann Internal Med 2002



Non-Paracetamol

Liver volume and Bx

Time from

all 3 of the following within 24 hrs

INR > 6.5

PT > 100 INR > 6.5<u>any 3 of :</u> Creatinine > 300 µmol/l seronegative hepatitis or grade 3 - 4 encephalopathy drug related / halothane Bilirubin > 300 μ mol/l Lactate : 4 hrs > 3.5 OR 43 p<0.001 INR > 3.5Age < 10 yrs or > 40 yrs Lactate : 12 hrs > 3.5 OR 63 p<0.001 J - E > 7 daysBudd Chiari : renal failure + HE Low P04 : good prognosis Clichy Criteria -Grade III + (Alpha feta protein) Factor V <30% + age > 30 MELD > 30Factor V < 20% + age < 30 **BiLE** score

Acute liver failure: Prognostication based on scores or biomarkers

King's College criteria : paracetamol and non-paracetamol ± lactate



Clichy criteria

MELD > 30

Gc-globulin, alpha-fetoprotein

BiLE criteria (bilirubin, aetiology, lactate)USA ALFindexLiver volume, liver % necrosis on Bx

Wilsons index

Use of prognostic models

 Critical to minimise 'unnecessary transplantation'



Meta-analysis of performance of Kings's College Hospital Criteria in prediction of outcome in non-paracetamol-induced acute liver failure



Fig. 4. Sensitivity/specificity plot showing changes in predictive behaviour in KCC for early (pre 1995), middle (1996-2005) and later (post 2005) eras demonstrating reduction in sensitivity with era with preservation of specificity. Ellipses subtend the 95% C for sensitivity and specificity for each era.

Journal of Hepatology 2010 vol. 53 j 492–499

Years	or-re	(919 ⁸³	, Beres	,98 ^{9,69}	, 98 ^{4,98}	,998-20 ^C	, popros
Beds (n)	2		5	6	10		15
Intensivi	st Staffing	(n)		1		23	4
ALF tran	splantation	n					\rightarrow
N-acetyl	cysteine						-
RRT	He	modialysis		Co	ntinuous I	hemofiltratio	n
ICH ther	ару			Manni	tol	30%	NaCl

Lessons from look-back in acute liver failure? A single centre experience of 3300 patients



Journal of Hepatology 2013

Fig. 3. Hospital survival in 2095 admissions with ALF by era. Error bars are 95% CI; p <0.00001.

Teams make things work julia.wendon@kcl.ac.uk

			MI -	R	N==A M.	1000
1.7.73 71	7575 Lyn	FILLING				
17. × 13 27	19764 Lind	Lecoca	31	Toda [humany]	FHF Ausunta phallositis	-
14· ×·73 3				Todd	w	C-14 - X-73 C-20-X-73 C-21 - X-73
					. 6	C - 12 - X- 73
23·×73.4 714	1187 June	THORNHILL	23	Anglesezo Carmento Honor Crement	- FITF - Unlopsing	
26. 2. 73 5 711	740 Sunh	Goodricht	23.	TOOD Emhiliogh Hospital	FHF - proverbund 0. d.	C 26 · X·73
1. N. 73 (7210	005 Colette	O'BRIEN .	51	st. Anne's General Hospital, Trickenhan	FUE - Hyplits A.	
· N1.73. 7 7210	ob Sally	GARBER	26.	Red hill General	FHF - Hyphilis A.	
· N. 73 972102	L Dunda	JACKSON	51	Kinyoton syn Themes Hisogifal	FHF - Hayalilia A.	C 8. X1.73 7 C 1. X(73 b

Variable	NBAClf (%)	BAClf (%)	P value	Inf	action	n ie d	r	nn	nn	n		
Median age Sex (males) On admission	n = 134 (65) 38 (28-48) 56/134 (42)	n = 72 (35) 39 (27–47) 31/72 (43)	in ALF & related to							′∎∎		
Respiratory rate Temperature (°C) MAP (mmHg) Heart rate On vasopressors White blood count	20 (16–26) 36.2 (1.4) 67 (58–80) 108 (80–122) 46/134 (34) 10.0 (6.1– 13.9)	18 (15–24) 35.8 (1.1) 67 (59–79) 107 (95–126) 22/72 (31) 9.9 (5.1–14.1)	0.13 0.44 0.85 0.49 0.80	Severity Karvellas Intensive Care Med 2009								
SIRS score SIRS score ≥ 2 PO ₂ /FiO ₂ ratio INR	1.0 (Table 2 Logistic regression model predicting mortality in all ALF 54/1 patients (using APACHEII to adjust for illness severity) 287 3.2 (Predictor Odds Standard 95% P value											
Ereatinine (mmol/l) Bilirubin (mmol/l) Lactate (mmol/l) Ammonia (µmol/l) pH	3.6 (103 Liver trai 7.4 (APACHE 7.4 Age	nsplant EII	ratio 0.20 1.09 1.41	error 0.09 0.03 0.20	CI 0.08-0.49 1.04-1.14 1.06-1.86	<0.0001 <0.0001 0.02		ПП	1 =	Ħ		
APACHEII Glasgow coma score During total LITU stay	17.6 Lactate 8 (6- Maximun	n HE grade	1.14 1.76	0.06 0.37	1.03–1.26 1.16–2.67	0.006 0.007	ropacter - Serratia -	omonas -	- WSSA -	MRSA	Other - Candida -	
RRT in LITU Days on RRT MV in LITU Days on MV Maximum HE grade >2	87/1: Odds ratios are expressed for APACHEII (incremental units), lac- 3 (0-tate (per 1 mmol/L). Odds ratio per 10-year deviation from the 103/ mean age 37.8 years. Maximum hepatic encephalopathy (HE) 5 (2-grade pre-intubation 84/11											
Length of LITU stay KCH criteria ^a Listed for transplant Fransplanted Survival ^b	7 (3–13) 69/134 (51) 41/134 (31) 33/134 (26) 86/134 (64)	26 (18–36) 39/72 (54) 27/72 (36) 26/72 (36) 45/72 (62.5)	<0.001 0.83 0.40 0.08 0.93	Etiology Fig. 2 Frequency of bacteraemia/fungaemia isolates in 72 ALF patients admitted to the Liver intensive therapy unit at King's College (January 2003–July 2005)								