5th East Midlands Critical Care

and Peri-Operative Medicine Conference

Crowne Plaza Hotel, Nottingham - 18th - 19th October 2018

Organised by Dr Sandeep Dhir Approved by the Royal College of Anaesthetists for 12 CPD credits



Day One



Liver Patients in ICU

Dr I Nesbitt Freeman Hospital October 2018

Introduction

- Blame Sandeep again
- Regional Centre
 - Liver transplant
 - HPB surgery



• Confession- I'm not that interested in liver disease....

A Talk of Two Halves

• General Points

• Specific Issues



Similar to other ICU patients

- Multi-organ involvement
- Nutrition
- Infection
- Weaning
- Rehabilitation
- Multi-disciplinary team
 - Wide spread of opinion
 - Evidence variable



Different from other ICU patients - and from each other

- GI bleed
 - (portal hypertension)
- Acute on chronic decompensation
 - (alcoholic hepatitis, encephalopathy)
- Incidental
 - (elective surgery)
- Post-operative
 - (small for size, ischaemic hepatitis)
- Fulminant failure
 - (specialist care/transplant)



Overall principles

- Identify liver disease
 - Culprit or bystander?
 - E.g. post CA ischaemic hepatitis
- Consider treatable disease
 - May need consultation/transfer
 - Budd-Chiari, Wilsons, viral disease, abscess, ASH
- Imaging/biopsy/clever blood tests

 USS/CT, doppler/angiography
 - Biopsy often unhelpful in critically ill

Jaundice/abnormal LFTs 1⁰ Liver Disease?

- Haemolysis
 - (Transfusion, haematoma)
- Drugs
 - (inc. anaesthetics, overdose, drug interactions)
- TPN

- (high CHO load-c.25% BR, AST, Alk phosp)

- MOF
 - (e.g. post Cardiac arrest ischaemic hepatitis)
- Infections
 - (HBV, HCV, Malaria, Weils etc.)
- Misc
 - Pregnancy, AIH, malignancy, mushrooms etc....

Is Liver Disease Bad?



Progression of Liver Disease



EV= varices, HPVG= Hepatic portal venous gradient,

HE= hepatic encephalopathy, ACLF= acute on chronic liver failure

Bad Outcomes-

Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies

Gennaro D'Amico^{1,*}, Guadalupe Garcia-Tsao², Luigi Pagliaro¹



Journal of Hepatology 44 (2006) 217-231

Bad Outcomes

Recent advances in clinical practice



Acute-on-chronic liver failure: an update

Ruben Hernaez,¹ Elsa Solà,^{2,3,4} Richard Moreau,^{5,6,7,8,9} Pere Ginès^{2,3,4}

Table 7 CLIF Consortium Organ Failure Score: simplified version of the CLIF-SOFA score							
Organ/ system	Variable	Score=1	Score=2	Score=3			
Liver	Bilirubin (mg/dL)	<6	6 to ≤12	>12			
Kidney	Creatinine (mg/dL)	<2	2 to <3.5	≥3.5 or RRT			
Brain	Encephalopathy grade (West-Haven)	0	1–2	34			
Coagulation	INR	<2	2 to <2.5	≥2.5			
Circulation	MAP (mm Hg)	≥70	<70	Vasopressors			
Respiratory	PaO ₂ /FiO ₂ or SpO ₂ /FiO ₂	>300 >357	≤300 and >200 >214 and ≤357	≤200 ≤214			

Highlighted areas indicate the definition of each organ failure. CLIF, chronic liver failure; FIO₂, fraction of inspired oxyger; INR, international normalised ratio; MAP, mean arterial pressure; PaO₂, partial pressure of arterial oxyger; RRT, renal replacement therapy; SOFA, Sequential Organ failure Assessment; SpO₂, pulse oxymetric saturation.



Bad outcomes 2

British Journal of Anaesthesia 97 (4): 496–8 (2006) doi:10.1093/bja/ael177 Advance Access publication July 18, 2006 BJA

CRITICAL CARE

One year outcome of intensive care patients with decompensated alcoholic liver disease

I. J. Mackle, D. G. Swann and B. Cook*

Table 2 Mortality in patients admitted to ICU with decompensated alcoholic liver disease

ICU mortality (%)	64/110 (58)
Hospital mortality (%)	77/109 (71)
6 month mortality (%)	83/106 (78)
12 month mortality (%)	86/106 (81)

Table 4 Mortality in organ failure and support subgroups. MV, mechanical ventilation; RRT, renal replacement therapy; Cr, Creatinine

	n	ICU mortality n (%)	Hospital mortality n (%)
MV (all)	103	62 (60)	74 (72)
MV (no other interventions)	26	1 (4)	8 (31)
Vasoactive drugs	77	62 (81)	66 (86)
Cr >120 μ mol litre ⁻¹	60	45 (75)	52 (87)
RRT	37	30 (81)	33 (89)
MV + vasoactive drugs	76	61 (80)	65 (86)
MV + RRT	35	29 (83)	31 (89)
Vasoactive drugs + RRT	35	30 (86)	32 (91)
MV + vasoactive drugs + Cr >120	52	43 (83)	46 (89)
MV + vasoactive drugs + RRT	34	29 (85)	31 (91)

Therapeutics	and Clinica	l Risk Management	open acce
Open Access Full Text Ar	on-chro	nic <mark>l</mark> iver failure:	a review
	ACLF grade	Characteristics	
		Acute liver damage associated with	
	Grade I	Single kidney failure [*] OR liver failure [*] , coagulopathy, ^c circulatory failure [*] , respiratory failure, [*] serum creatinine 1.5–1.9 mg/dL and/or mild to moderate hepatic encephalopathy OR brain fuilure [®] with creatinine 1.5–1.9 mg/dL	
	Grade 2	Two organ failures	
	Grade 3	Three or more organ failures	
	liver damage; this scorr experience) per orgat therapy: *total bilirubir 20 × 10 ³ /L: 4use of dopa *PaO/FIO ₂ = 200 mg/dL or IV. Data from from 1 Abbreviations: ACLF SOFA, Sequential Orga	e was validated to be used in this study, based on auth n: "serum creatinine ≥ 2 mg/dL or kidney replacen $a \geq 12$; "international Normalized Ratio ≥ 2.5 or plat mine, dobutamine, terlipressin, norepinephrine, epineph or SpO_/FIO_ ≤ 214 mg/dL; "hepatic encephalopathy graw Moreau et al." a scute-on-chronic liver failure; CLIF, Chronic Liver Fai n Failure Assessment.	nors' nent elets erine: de III lure:
Table 2			
Subgroups	1	fortality rate	Mortality rate
	a	at 28 days	at 90 days
ALD alone ^a	4	.7%	14%
ACLF grade 1	2	2.1%	40.7%
ACLE - 1 2	3	17%	52 3%
ACLF grade Z	J	2/0	JZ.J/0

Notes: CLIF-SOFA criteria: *ALD without organ failure or ALD with only one organ failure (liver, circulatory, or respiratory failure, or coagulopathy), other than kidney failure, and without encephalopathy, or ALD and brain failure with serum creatinine ≤ 1.5 mg/dL. Data from Moreau et al.¹¹

Abbreviations: ACLF, acute-on-chronic liver failure; ALD, acute liver disease; CLIF, Chronic Liver Failure; SOFA, Sequential Organ Failure Assessment.

The more organ support you need, the worse your outcome is, One Table 2 Mortality in patients admitted liver disease ICU mortality (%) Hospital mortality (%) 6 month mortality (%) 12 month mortality (%) Table 4 Mortality in organ failure and support subgroups. MV, mechanic ventilation; RRT, renal replacement therapy; Cr, Creatinine ortality rate

ACLF grade 3

Notes: CLIF-SOFA criteria: *ALL

organ failure (liver, circulatory, or respi-

kidney failure, and without encephalopathy,

creatinine ≤1.5 mg/dL. Data from Moreau et al. Abbreviations: ACLF, acute-on-chronic liver failur

CLIF, Chronic Liver Failure; SOFA, Sequential Organ Failur

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Are Outcomes improving?



Improving survival by cohort

Increased Survival for Patients With Cirrhosis and Organ Failure in Liver Intensive Care and Validation of the Chronic Liver Failure–Sequential Organ Failure Scoring System

Mark J. W. McPhail, ** Debbie L. Shawcross, * Robin D. Abeles, * Anthony Chang, * Vishal Patel, * Guan-Huei Lee, * Maheeba Abdulla, * Elizabeth Sizer, * Christopher Willars, * Georg Auzinger, * William Bernal, * and Julia A. Wendon*



Clinical Gastroenterology and Hepatology 2015;13:1353–1360

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Does Presentation Matter?







Presentation & survival

Clinical Course of Alcoholic Liver Cirrhosis: A Danish Population-Based Cohort Study

Peter Jepsen,1,2 Peter Ott,2 Per Kragh Andersen,3 Henrik Toft Sørensen,1 and Hendrik Vilstrup2



Hepatology. 2010;51:1675-1682

General Points- So Far

- Liver disease is bad
- Complications = worse
- More failing organs = even worse
- ICU outcomes are improving









Specific Points



Acute on Chronic Disease: A multi-system disease

- Cirrhosis, NASH, ALD/ASH, Wilsons etc.
 - Hyponatremia, hyper-ammonaemia (cerebral injury)
 - Portal hypertension (bleeding, SBP)
 - Immune suppression & inflammatory state (infection)
 - Reduced glutathione (drug handling)
 - Dysfunction:
 - Coagulation
 - Renal
 - Adrenal

Hyponatremia is bad

RESEARCH

Open Access

Hyponatremia influences the outcome of patients with acute-on-chronic liver failure: an analysis of the CANONIC study



Hyponatremia = <135mmol/l , or <130mmol/l with ascites

Hypervolaemic hyponatremia- retained Na and H2O

Sodium restriction, diuretics, (V2 antagonist tolvaptan)

Cárdenas et al. Critical Care (2014) 18:700

Renal Impairment (also bad)

- Common (40-50%)
- Multifactorial
 - HRS- (c. 10%) assumed present
 - Volume replacement
 - Vasoconstrictors
 - Terlipressin /Noradrenaline
- Increases mortality



Renal Replacement

- Citrate a/c with liver failure
 - Seems safer than thought
- Measuring citrate
 - Possible but unlikely to help
- Various regimes
 - Low Ca²⁺: Ca ratio

RESEARCH	Open Access
Long-term continuous renal replacement therapy and anticoagulation with citrate in critically ill patients with severe liver dysfunction	CrossMari

Klingele et al Critical Care 2017. 21. 294

RESEARCH	Open Access
Safety and efficacy of regional citrate	Cualler .
hemodialysis in the presence of liver	S
failure: the Liver Citrate Anticoagulation	
Threshold (L-CAT) observational study	

Slowinski et al. Critical Care 2015. 19. 349

• Toxicity: Accumulation v excretion?

Albumin (good-ish)

- Traditional use
- Volume expansion

 HRS, CVS stability for paracentesis
- Immune modulating
 - ?reduces bacterial translocation/SBP
- But evidence base frequently weak



Adrenal dysfunction

- Common
 - in liver disease
 - in critically ill
 - ? 30% overall
- No consensus
 Definition or management



Suggest: add if vasoconstrictors escalating

ASH & Alcoholic hepatitis (really bad)

- Syndrome overlap/diagnosis
 - NASH, Cirrhosis
 - Probably a subgroup has a different disease
 - » Different therapeutic options in future
- Management
 - General care
 - Prophylactic Antibiotics
 - Probably
 - Steroids
 - Inconsistent benefit
 - In most severe disease only?



GI Bleeding (could be worse)

- Banding> sclerotherapy
- Transfusion limits- 7g/dl
- Platelets- > 50-70?
- Feeding- good nutrition
- Prophylactic antibiotics
- Post endoscopy PPI infusion
- TIPSS- early
- ? Self-expanding stents



Villanueva et al. NEJM 2013. 368. 11-21



Lau et al. NEJM 2000. 343. 310-16

Early TIPSS

The NEW ENGLAND JOURNAL of MEDICINE ORIGINAL ARTICLE Early Use of TIPS in Patients with Cirrhosis and Variceal Bleeding

Juan Carlos García-Pagán, M.D., Karel Caca, M.D., Christophe Bureau, M.D.,



Long term benefit 86% v 61% 2 year survival

Garcia-Pagan et al. N Engl J Med 2010;362:2370-9.

Acute Liver Failure (very bad)

- Jaundice, encephalopathy, coagulopathy
- Hyperdynamic CVS & MOF
- Cerebral Oedema
 - Airway protection/sedation/+-NMB
 - Early RRT
 - (Mannitol, Hypertonic saline)
- Coagulopathy until listed for OLTx
- Glucose/NAC/(ICP monitors)

Practical procedures

- Coagulopathy and procedures
 - USS guided procedures/FFP
- Antifungals
 - Adjust/choose drug for renal function
- SBP
 - Ascitic tap, low threshold for Abx
- Ascitic drains (USS/landmark)
 - Albumin (weak evidence for low volume <5L)

Specific Interventions

- NAC
 - Even for non-POD Rx- but evidence poor
- Rifampicin
 - Enzyme inducer (or voodoo)
- Lactulose v rifaximin
 - Marginal benefit
- More Voodoo
 - RRT for ammonia, defibritide for VOD, High volume PEX
- Liver support
 - MARS, Liver assist, pig livers,
 - 3D organ printing...

Surgery

- Surgical patients
 - Liver resection
 - Small for size
- Liver Transplant
 - Kings Criteria (flexible)
 - MDT decision & discussion



Decision Making

- Who to admit?
- What to do?
- When to stop?



Admission

Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies

Gennaro D'Amico^{1,*}, Guadalupe Garcia-Tsao², Luigi Pagliaro¹



Journal of Hepatology 44 (2006) 217-231

Admission

- Reversibility
- Functional state
- Physiological Reserve
- Compliance with Rx
- Social support
- Previous admissions
- Disease trajectory

Escalation & Ongoing Management

- Requirement for Organ support
 - Cardiovascular
 - Respiratory
 - Renal
- Scorings systems as predictors
 - At all
 - Time based
- Compared with other diseases
 (e.g. Haem-onc day 5 SOFA)

Scoring systems- six of one...

(SAGE

Original article	Ģjics
	Journal of the Intensive Care Society
	2017, Vol. 18(1) 24-29
Alcoholic liver disease on the	© The Intensive Care Society 2016
Alcoholic liver disease on the	Reprints and permissions:
	sagepub.co.uk/
Intensive care unit – Outcomes	journalsPermissions.nav
	DOI: 10.1177/1751143716662055
and prognostication	jics.sagepub.com
and progression	(C) CACE

James I Beck¹, Anca Staicu², Simon M Everett³ and Phil Jackson⁴

Recent advances in clinical practice



Acute-on-chronic liver failure: an update Ruben Hemaez,¹ Elsa Solà,^{2,3,4} Richard Moreau,^{5,6,7,8,9} Pere Ginès^{2,3,4}

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A Prediction of 28-day mortality B Prediction of 90-day mortality

Table 6. Area under the receiver-operator curve. SOFA ICU admission vs. ICU mortality 0.76 SOFA ICU admission vs. hospital mortality 0.69 SOFA at 48 hr vs. ICU mortality 0.74 SOFA at 48 hr vs. hospital mortality 0.71 MELD ICU admission vs. ICU mortality 0.67 MELD ICU admission vs. hospital mortality 0.63 MELD 48 hr vs. ICU mortality 0.72 MELD 48 hr vs. hospital mortality 0.68

ROC: approx 0.7



	0.8 -			کس		/		
itivity	0.6		ſ			r		
Sens	0.4 -		H	/		— c	LIF-C ACLF	s
	0.2		/			— M — M	ELDs ELD-Nas Ps	
	0.0	<u>/</u>						
	0	.0	0.2	0.4	0.6	0.8	1.0	
			1	Speci	ficity			

		AUROC (95% CI)	p value; vs; CLIF-C ACLF			AUROC (95% CI)	p value; vs; CLIF-C ACLF
_	CLIF-C ACLFs	0.79 (0.73-0.85)		_	CLIF-C ACLFs	0.76 (0.70-0.83)	
_	MELDs	0.70 (0.62-0.77)	0.0089	_	MELDs	0.65 (0.58-0.72)	0.0014
_	MELD-Nas	0.70 (0.62-0.77)	0.0097	_	MELD-Nas	0.67 (0.60-0.74)	0.0082
_	CPs	0.70 (0.63-0.77)	0.0075	_	CPs	0.69 (0.62-0.75)	0.0301

Suggested management

Recent advances in clinical practice



Cultural aspects

- Prognostic Pessimism perhaps the greatest variable
 - Self inflicted
 - Futile
 - Costly
 - Distributive justice
- cf. EoLC, COPD, Haem-Onc
- Even with EBM, every patient is different

The Bottom Line

• Your liver gets better or you get a better liver



Summary

- Increasing ICU admissions with liver disease
- Improving survival rates
- Still high mortality rates
 Precipitant cause important
- Multi system disease

– High SOFA= high mortality

- Specific interventions help (e.g. TIPSS, OLTx)
- Active research (MARS/ELAD)
- MDT approach important

