Intensive care of the patient with Liver disease

Dr Donal Ryan
Consultant Intensivist, SVUH.
Introduction

- Patients with established Liver disease (cirrhosis)/end-stage, acute on chronic liver failure
  - Acute variceal bleed
  - Septic shock
  - Renal failure
  - Severe encephalopathy
  - All of the above

- Patients with Acute liver failure

- Patients post OLT
• AoCLF refers to an acute deterioration of liver function and subsequently other end organs over a period of weeks following a precipitating event (by an indirect [e.g., variceal hemorrhage, sepsis] or a direct [e.g., drug induced, liver resection] hepatotoxic factor) in a patient with previously well- or reasonably well-compensated chronic liver disease.

• ‘end- stage liver disease’ refers to a chronically decompensated patient due to relentless progressive deterioration of the underlying chronic liver disorder.
substantial overlap exists between these two entities in terms of clinical presentation

- jaundice,
- hepatic encephalopathy,
- hyperdynamic circulatory state
- hepatorenal syndrome

the main difference between them is the potential for recovery, the presence or absence of a precipitating event and the substantial evolution towards multiorgan failure
bacterial products are presumed to be a prerequisite to the development of infection, which is the cause of admission in 30–50% of patients. Infection is associated with the ensuing end-organ dysfunction by a range of mechanisms, including tissue damage caused by invading microbes locally, destruction of damaged tissue, and repair damage. If the initiating infectious or noninfectious factors overwhelm the local response, the local response becomes exaggerated, thus leading to further aggravation and ultimately to the inability to maintain homeostasis. This unbalanced reaction to these initiating injuries coalesces both an acute potentially life-threatening insult and a clear precipitant. Differentiation from a patient with end-stage liver disease and problems in determining the ideal moment and/or necessity or usefulness of certain therapeutic interventions is hampered. Although in theory the currently used working definition of acute-on-chronic liver failure (AoCLF) characterizes both a local proinflammatory and anti-inflammatory reaction caused by the host's imbalanced reaction to these initiating injuries, the pathogenesis, clinical manifestations, and potential therapeutic interventions are only a handful prospective studies available. With regard to prognosis, AoCLF also poses problems since it is caused by the host's imbalanced reaction to these initiating injuries, which is further aggravated and ultimately leads to the inability to maintain homeostasis.
• ICU mortality for patients with underlying cirrhosis is unchanged in the last 20 years

• The presence of two failing organ systems increases the mortality to 55%, whereas those who develop failure of three or more organs have almost 100% mortality.
Figure 3. Correlation between inhospital mortality and the number of nonhematologic organ failures on day 1 or after 3 days spent in the intensive care unit.

Cirrhotic patients in the medical intensive care unit: Early prognosis and long-term survival*

Vincent Das, MD, PhD; Pierre-Yves Boelle, PhD; Arnaud Galbois, MD; Bertrand Guidet, MD, PhD; Eric Maury, MD, PhD; Nicolas Carbonell, MD; Richard Moreau, MD, PhD; Georges Offenstadt, MD
• 'in select cirrhotic patients, intensivists may propose a trial of unrestricted intensive care for a few days, followed by withdrawal or limitation of life-sustaining treatments in the case of persistence of a high degree of organ failure after this delay'
• In patients only in need of mechanical ventilation, the 90-day mortality was 76%.

• If respiratory failure was further complicated by shock treated with vasopressor agents, the 90-day mortality increased to 89%.

• Ninety-day mortality for patients in need of mechanical ventilation, vasoactive medication, and renal replacement therapy because of acute kidney injury was 93%.

The outcome of critical illness in decompensated alcoholic liver cirrhosis

M. Kavli, T. Strom, M. Carlsson, B. Dahler-Eriksen and P. Toft
Department of Anesthesia and Intensive Care Medicine, Odense University Hospital, University of Southern Denmark, Odense, Denmark
Any predictors of favourable outcome?

• ‘Admission for elective intubation during acute variceal bleeding and for isolated episodes of hepatic encephalopathy (grade 3 or above) in the absence of significant metabolic disarray, in our experience do well and ICU admission is wholly justified’

Outcome of patients with cirrhosis admitted to intensive care
Mark J. Austin and Debbie L. Shawcross

Liver Intensive Therapy Unit, Institute of Liver Studies, King’s College Hospital, London, UK

Current Opinion in Critical Care 2008, 14:202–207
Main reasons for ICU admission

• Acute variceal bleed
• Septic shock
• HRS/Renal replacement therapy
• Severe encephalopathy
• All the above
Variceal haemorrhage

• Much less common than non-variceal haemorrhage but often more dramatic

• 3 main areas of management:
  • primary prophylaxis to prevent a first episode of variceal hemorrhage,
  • treatment of the acute bleeding episode,
  • secondary prophylaxis (prevention of recurrent variceal hemorrhage).
Case History

• 61 yo male

• History of non-cirrhotic portal hypertension (?portal thrombosis)

• Prophylactic oesophageal banding

• 3 weeks later - presentation with haematemesis (500 mls) at a regional hospital

• Initially stable - transferred to ward (SVUH)
• Massive GI bleed on ward 2/7 post admission

• Oesophageal banding attempted - unsuccessful

• Sengstaken Blakemore tube inserted as a temporising measure - admitted to ICU for resuscitation prior to surgical portocaval shunt insertion

• 5 L blood loss - 13 u RCC, 2 pools platelets, 4g fibrinogen, 5 units octaplas
• Massive GI bleed on ward 2/7 post admission

• Oesophageal banding attempted - unsuccessful

• Sengstaken Blakemore tube inserted as temporising measure - admitted to ICU for resuscitation prior to surgical portocaval shunt insertion

• 5 L blood loss - 13 u RCC, 2 pools platelets, 4 g fibrinogen, 5 units octaplas
Fig. 1. Chest radiograph shows gastric balloon of SB tube (arrow) in the left hemithorax.

Fig. 2. Computed tomography of chest demonstrates SB tube (arrow) penetrated throughout the middle third of esophageal wall (from the level of T5-T9) to the left pleural cavity.
• 2 days post ICU discharge, further massive variceal bleed

• Hypotensive

• Emergency OT for oesophageal transection

• Further massive transfusion

• Discharged 3 weeks later to his base hospital
The 6-week mortality with each episode of variceal hemorrhage is approximately 15 to 20%,

- 0% among patients with Child class A disease
- approximately 30% among patients with Child class C disease
Initial Resuscitation

• Should I intubate this patient prior to endoscopy?

• What haemodynamic targets are appropriate in a patient with portal hypertension?

• What Hb target should I aim at?

• What does the INR mean in cirrhotic patients? How will I correct the coagulopathy?
Initial Resuscitation

- Should I intubate this patient prior to endoscopy?

- What haemodynamic targets are appropriate in a patient with portal hypertension?

- What Hb target should I aim at?

- What does the INR mean in cirrhotic patients? How will I correct the coagulopathy?
• Risk of aspiration with an acute variceal bleed 2.4-3.3%

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intubated (n = 47)</th>
<th>Nonintubated (n = 22)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of hematemesis (%)</td>
<td>87</td>
<td>82</td>
<td>NS</td>
</tr>
<tr>
<td>Encephalopathy (% grade I)</td>
<td>23</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td>Active bleeding (%)</td>
<td>53</td>
<td>64</td>
<td>NS</td>
</tr>
<tr>
<td>Endoscopic therapy (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVL</td>
<td>92</td>
<td>60</td>
<td>0.006</td>
</tr>
<tr>
<td>SCL</td>
<td>6</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>EVL + SCL</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

Risk of Aspiration Pneumonia in Suspected Variceal Hemorrhage: The Value of Prophylactic Endotracheal Intubation Prior to Endoscopy

David G. Koch · Miguel R. Arguedas · Michael B. Fallon
The two cohorts were also clinically similar at the time of admission (Table 2). All patients had less than grade II encephalopathy and were considered to be able to protect their airway as per the inclusion criteria for the study. Specifically, grade I encephalopathy was present in 23% of both intubated and nonintubated patients. A history of hematemesis was present in 41 of 47 (87%) episodes of VH among the patients who were intubated, compared to 18 of 22 (82%) episodes among patients who were not intubated ($P = \text{NS}$).

ET intubation was performed by an Anesthesiology resident in 29 (62%) episodes, whereas in 6 (13%) episodes the procedure was done by Critical Care fellows, and in 12 (25%), by Medicine residents.

All patients had EGD performed within 12 hr of admission to the ICU and pharmacological therapy had been initiated in all episodes at least 30 min prior to endoscopy (mean: $1 \pm 2$ hr). All patients had active bleeding, with red blood documented in the stomach. Endoscopic findings are summarized in Table 2. Active hemorrhage was documented in 25 of 47 (53%) episodes among patients intubated and 14 of 22 (64%) of patients not intubated ($P = \text{NS}$). Endoscopic therapy (EVL and/or SCL) was performed in all episodes of VH. Although EVL was the therapeutic modality of choice, SCL was more commonly performed among nonintubated patients ($P = 0.006$). Hemostasis was successfully obtained in 43 of 47 (91%) among the intubated cohort vs. 20 of 22 (91%) in the nonintubated cohort ($P = \text{NS}$).

Table 3 summarizes the outcomes of intubation and VH. Both the occurrence of aspiration and the mortality were higher in the patients who underwent prophylactic intubation. Among patients who were intubated, aspiration pneumonia occurred in 9 of 47 (19%) episodes of VH, as opposed to 0 of 22 episodes among patients who were not intubated ($P = 0.01$). Of the patients who aspirated, five (56%) were intubated by an Anesthesiology resident, while three (20%) intubations were performed by Medicine residents, and one (13%) by Critical Care fellows. We found no association between the training of the person performing ET intubation and the risk of aspiration ($P = \text{NS}$). Among intubated patients in whom aspiration did not occur, the ET tube remained in place for $1.2 \pm 1$ day, whereas in those who aspirated, ventilatory support was necessary for $6.5 \pm 9$ days. The average length of stay per episode of VH in patients who underwent ET intubation was $8.2 \pm 6$ days, vs. $6.9 \pm 7$ days for ortho intubated ($P = \text{NS}$). Overall, 9 of 42 (21%) patients in the intubation group died, compared to only 1 of 20 (5%) patients who was not intubated ($P = \text{NS}$). Sepsis was considered the cause of death in the latter patient. Aspiration was considered the immediate cause of death among five of nine patients (56%), followed by sepsis (two patients), uncontrolled GI bleed (one patient), and progressive renal failure after the completion of endoscopy (one patient).

Discussion

The results of this study suggest that elective ET intubation as a prophylactic measure prior to endoscopy for suspected VH is associated with a substantial risk for aspiration and subsequent increased mortality. This outcome occurred independent of the mode of presentation (i.e., history of hematemesis), severity of bleeding (i.e., active/recent bleeding at the time of EGD), and level of training of the person performing ET intubation.

The results of our study contrast with the findings of Rudolph et al., who evaluated intubation prior to endoscopy for suspected VH in a single-center study of patients with a median age of 71 years and a median body mass index of 27. In this study, very few patients aspirated, and only 2 of 21 patients died. However, 11 of 21 patients were intubated by residents of internal medicine. This is in contrast with our findings, where the majority of intubations were performed by anesthesiology residents. These findings suggest that the risk of aspiration may be higher in patients intubated by non-anesthesiology residents.
The two cohorts were also clinically similar at the time of admission (Table 2). All patients had EGD performed within 12 hr of admission to the ICU and pharmacological therapy had been initiated in all episodes at least 30 min prior to endoscopy. The results of our study contrast with the findings of Rudolph et al., who evaluated intubation prior to endoscopy while performing ET intubation.

Aspiration occurred in 9 of 47 (19%) episodes of VH, pneumonia occurred in 9 of 47 (19%) episodes of VH, and sepsis occurred in 4 of 47 (8.5%) episodes of VH. Both the occurrence of aspiration and the mortality associated with aspiration were higher in the patients who underwent prophylactic ET intubation (8.2 days vs. 6.9 days, P < 0.01). Of the patients who aspirated, ventilatory support was necessary for those who aspirated, and among patients who were intubated, aspiration occurred in 22 of 47 (46.8%) episodes among patients intubated and nonintubated patients. A history of hematemesis was present in 41 of 47 (87%) episodes of VH among the intubated and nonintubated patients. A history of hematemesis, severity of bleeding (i.e., active/recent bleeding), and grade I encephalopathy were similar in both groups (Table 3). Grade II encephalopathy was present in 23% of both groups and were considered to be able to protect their airway as per the inclusion criteria for the study. Specifically, grade II encephalopathy was present in 23% of both groups.

The results of this study suggest that elective ET intubation should be considered in patients at high risk for aspiration and pneumothorax, such as patients with portal hypertension. Among patients who were intubated, aspiration occurred in 43 of 47 (91%) among the intubated cohort vs. 20 of 22 (82%) of those who aspirated among patients who were not intubated. In patients who aspirated, ventilatory support was necessary for 14 of 22 (64%) of patients not intubated (results reported per patients (Table 3). Table 4 summarizes the outcomes of intubation and clinical outcomes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intubated 47 episodes</th>
<th>Nonintubated 22 episodes</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration, n (%)</td>
<td>7 (17%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>9 (21%)</td>
<td>1 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Length of stay (days; mean ± SD)</td>
<td>N/A 8.2 ± 6</td>
<td>N/A 6.9 ± 7</td>
<td>NS</td>
</tr>
</tbody>
</table>

Only applies to patients with < grade 1 encephalopathy.
Initial Resuscitation

• Should I intubate this patient prior to endoscopy?

• What haemodynamic targets are appropriate in a patient with portal hypertension?

• What Hb target should I aim at?

• What does the INR mean in cirrhotic patients? How will I correct the coagulopathy?
change in portal pressure with volume expansion to maintain MAP>80 mmHg - Morales Hepatology 2003
• Target

• SBP - 90-100 mmHg

• HR < 100/min
Initial Resuscitation

• Should I intubate this patient prior to endoscopy?

• What haemodynamic targets are appropriate in a patient with portal hypertension?

• What Hb target should I aim at?

• What does the INR mean in cirrhotic patients? How will I correct the coagulopathy?
• PRBC transfusion should be done conservatively at a target hemoglobin level between 7 and 8 g/dl., although transfusion policy in individual patients should also consider other factors such as co-morbidities, age, hemodynamic status and ongoing bleeding


• Transfuse patients with massive bleeding with blood, platelets and clotting factors in line with local protocols for managing massive bleeding.
Initial Resuscitation

- Should I intubate this patient prior to endoscopy?

- What haemodynamic targets are appropriate in a patient with portal hypertension?

- What Hb target should I aim at?

- **What does the INR mean in cirrhotic patients? How will I correct the coagulopathy?**
The Coagulopathy of Chronic Liver Disease

Armando Tripodi, Ph.D., and Pier Mannuccio Mannucci, M.D.
Offer platelet transfusion to patients who are actively bleeding and have a platelet count of less than $50 \times 10^9$/litre.

Offer fresh frozen plasma to patients who have either:

1 - a fibrinogen level of less than 1g/litre, or

2 - a prothrombin time (international normalised ratio) or activated partial thromboplastin time greater than 1.5 times normal.

• Do not use recombinant factor Vlla except when all other methods have failed

• NICE clinical guidelines
Baveno V statement

Recommendations regarding management of coagulopathy and thrombocytopenia cannot be made on the basis of currently available data.

PT/INR is not a reliable indicator of the coagulation status in patients with cirrhosis
### Medical treatment pre endoscopy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose</th>
<th>Duration</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoconstrictor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octreotide</td>
<td>Intravenous 50-µg bolus, followed by infusion of 50 µg/hr</td>
<td>2–5 days</td>
<td>Bolus can be repeated in first hr if variceal hemorrhage uncontrolled; if rebleeding occurs during therapy, consider TIPS</td>
</tr>
<tr>
<td>Terlipressin</td>
<td>2 mg given intravenously every 4 hr for first 48 hr, followed by 1 mg given intravenously every 4 hr</td>
<td>2–5 days</td>
<td>If rebleeding occurs during therapy, consider TIPS</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>Intravenous 250-µg bolus, followed by infusion of 250–500 µg/hr</td>
<td>2–5 days</td>
<td>Bolus can be repeated in first hr if variceal hemorrhage uncontrolled; if rebleeding occurs during therapy, consider TIPS</td>
</tr>
<tr>
<td>Vapreotide†</td>
<td>Intravenous 50-µg bolus, followed by infusion of 50 µg/hr</td>
<td>2–5 days</td>
<td>If rebleeding occurs during therapy, consider TIPS</td>
</tr>
<tr>
<td>Antibiotic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Intravenous ceftriaxone at a dose of 1 g once a day</td>
<td>5–7 days or until discharge</td>
<td>No long-term antibiotics unless spontaneous bacterial peritonitis develops</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>400 mg given orally twice a day</td>
<td>5–7 days or until discharge</td>
<td>No long-term antibiotics unless spontaneous bacterial peritonitis develops</td>
</tr>
</tbody>
</table>
Efficacy of Oral Norfloxacin and IV Ceftriaxone in the Prevention of Bacterial Infections in Patients With High Risk of Infection Development

Thirty-five patients (20 in the norfloxacin group and 15 in the ceftriaxone group) had at least 1 independent predictor of proved or possible infection development and were considered to have a high risk of infection. Twenty-nine patients (16 in the norfloxacin group and 13 in the ceftriaxone group) had transfusion requirements of 2 units and 15 (9 and 6, respectively) had failure to control the bleeding within the first 24 hours.

Ten out of 20 high-risk patients in the norfloxacin group (50%) developed proved or possible bacterial infections within the first 10 days following inclusion. In contrast, this only occurred in 2 out of 15 (13%) patients in the ceftriaxone group (P=0.02).

Probability curves of proved plus possible and proved bacterial infections in these 2 groups are shown in Figure 4. Significant differences were observed between groups.

Figure 2. Probability of remaining free of proved and possible infections (A) and proved infections (B) in patients receiving ceftriaxone (continuous line) and norfloxacin (dotted line). There were significant differences between groups.

Figure 3. Probability of remaining free of spontaneous bacterial peritonitis or bacteremia in patients receiving ceftriaxone (continuous line) and norfloxacin (dotted line). There were significant differences between groups.

Table 3. Proved and Possible Bacterial Infections and Organisms Isolated in the Study

<table>
<thead>
<tr>
<th></th>
<th>Ceftriaxone (n=54)</th>
<th>Norfloxacin (n=57)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with proved or possible infections</td>
<td>6 (11)</td>
<td>19 (33)</td>
<td>0.01</td>
</tr>
<tr>
<td>Patients with proved infections</td>
<td>6 (11)</td>
<td>15 (26)</td>
<td>0.07</td>
</tr>
<tr>
<td>Type of infection:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary infection</td>
<td>3 (6)</td>
<td>8 (14)</td>
<td>ns</td>
</tr>
<tr>
<td>Spontaneous bacteremia</td>
<td>0</td>
<td>4 (7)</td>
<td>ns</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis</td>
<td>1 (2)</td>
<td>3 (5)</td>
<td>ns</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>ns</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organisms, n</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fermentative gram-negative bacilli</td>
<td>0</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>05</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>01</td>
</tr>
<tr>
<td>Non fermentative gram-negative bacilli</td>
<td>1</td>
</tr>
<tr>
<td>Pseudomonas aeruginosas</td>
<td>10</td>
</tr>
<tr>
<td>Alcaligenes faecalis</td>
<td>01</td>
</tr>
<tr>
<td>Gram-positive cocci</td>
<td>3</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>01</td>
</tr>
<tr>
<td>Streptococcus viridans</td>
<td>02</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
<td>01</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>1</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>02</td>
</tr>
</tbody>
</table>
Variceal endoscopic management

Ligation (EVL) is the recommended form of endoscopic therapy for acute oesophageal variceal bleeding.

Endoscopic therapy with tissue adhesive (e.g. N-butyl-cyanoacrylate) is recommended for acute bleeding from isolated gastric varices (IGV) and those gastro-oesophageal varices type 2 (GOV2) that extend beyond the cardia.
TIPS

• Salvage therapy for the 10 to 20% of patients in whom standard medical therapy fails

• 2 RCTS - early placement of a shunt (within 24 to 48 hours after admission) a/w significant improvement in survival among high-risk patients (i.e., patients with an HVPG >20 mm Hg or with Child class C disease with a score between 10 and 13 points)

• The decision to use this approach as salvage therapy in this high-risk population should be made sooner rather than later.
An early TIPS within 72 h (ideally <24 h) should be considered in patients at high-risk of treatment failure (e.g. Child-Pugh class C >14 points or Child class B with active bleeding) after initial pharmacological and endoscopic therapy.
Surgical management

• Mesocaval shunts

• Oesophageal transection or oesophageal devascularisation

• Surgical portosystemic shunts ‘non-inferior’ to TIPS in Cochrane review 2006

• Usually reserved for patients in whom TIPS is contraindicated or has not been successful.
Standard resuscitation principles

+ 

Appropriate medical therapy

+ 

Specialist referral

= 

Improved outcome?
Sepsis

- Septic and cirrhotic phenotypes similar
- Source control vital but site of infection may not be obvious
- WCC/CRP may not be elevated
- Culture all available sites
- Assume there is an infection even when it is hard to find
Septic shock

- Survival from septic shock is especially poor, even when resuscitation is quickly and appropriately initiated

- Fernandez (Hepatology 2006), in an historical case control study, found that administration of low dose steroids to septic cirrhotic patients resulted in a reduced time to shock reversal and improved survival

- Arabi (CMAJ 2010). 75 cirrhotic patients.

- Relative adrenal insufficiency was diagnosed in 76% of patients.

- Steroid- significant reduction in vasopressor doses and higher rates of shock reversal.

- not associated with a reduction in 28-day mortality but was associated with an increase in shock relapse and gastrointestinal bleeding
Hydrocortisone Therapy for Patients with Septic Shock

Charles L. Sprung, M.D., Djillali Annane, M.D., Ph.D., Didier Keh, M.D., Rui Moreno, M.D., Ph.D., Mervyn Singer, M.D., F.R.C.P., Klaus Freivogel, Ph.D., Yoram G. Weiss, M.D., Julie Benbenishty, R.N., Armin Kalenka, M.D., Helmuth Forst, M.D., Ph.D., Pierre-Francois Laterre, M.D., Konrad Reinhart, M.D., Brian H. Cuthbertson, M.D., Didier Payen, M.D., Ph.D., and Josef Briegel, M.D., Ph.D., for the CORTICUS Study Group*

Abstract

From Hadassah Hebrew University Medical Center, Jerusalem (C.L.S., Y.G.W., J. Benbenishty); Raymond Poincaré Hospital, University of Versailles, UniverSud Paris, Garches, France (D.A.); Charité Universitätsmedizin Berlin, Campus Virchow-Klinikum, Berlin (D.K.); Hospital de St. António dos Capuchos, Centro Hospitalar de Lisboa Central, Lisbon, Portugal (R.M.); Bloomsbury Institute of Intensive Care Medicine, University College London, London (M.S.); Analytica International, Loerrach, Germany (K.F.); Klinikum Mannheim, Mannheim, Germany (A.K.); Zentralklinikum Augsburg, Augsburg, Germany (H.F.); St. Luc University Hospital, Université Catholique de Louvain, Brussels (P.-F.L.); Friedrich Schiller Universität, Jena, Germany (K.R.); Health Services Research Unit, University of Aberdeen, Aberdeen, United Kingdom (B.H.C.); Hôpital Lariboisière, Denis Diderot University of Paris, Paris (D.P.); and Klinikum der Universität, Ludwig Maximilians Universität, Munich, Germany (J. Briegel). Address reprint requests to Dr. Sprung at the General Intensive Care Unit, Department of Anesthesiology and Critical Care Medicine, Hadassah Hebrew University Medical Center, P.O. Box 12000, Jerusalem, Israel 91120, or at sprung@cc.huji.ac.il.

*Members of the Corticosteroid Therapy of Septic Shock (CORTICUS) study group are listed in the Appendix.


Background

Hydrocortisone is widely used in patients with septic shock even though a survival benefit has been reported only in patients who remained hypotensive after fluid and vasopressor resuscitation and whose plasma cortisol levels did not rise appropriately after the administration of corticotropin.

Methods

In this multicenter, randomized, double-blind, placebo-controlled trial, we assigned 251 patients to receive 50 mg of intravenous hydrocortisone and 248 patients to receive placebo every 6 hours for 5 days; the dose was then tapered during a 6-day period. At 28 days, the primary outcome was death among patients who did not have a response to a corticotropin test.

Results

Of the 499 patients in the study, 233 (46.7%) did not have a response to corticotropin (125 in the hydrocortisone group and 108 in the placebo group). At 28 days, there was no significant difference in mortality between patients in the two study groups who did not have a response to corticotropin (39.2% in the hydrocortisone group and 36.1% in the placebo group, \(P=0.69\)) or between those who had a response to corticotropin (28.8% in the hydrocortisone group and 28.7% in the placebo group, \(P=1.00\)). At 28 days, 86 of 251 patients in the hydrocortisone group (34.3%) and 78 of 248 patients in the placebo group (31.5%) had died (\(P=0.51\)). In the hydrocortisone group, shock was reversed more quickly than in the placebo group. However, there were more episodes of superinfection, including new sepsis and septic shock.

Conclusions

Hydrocortisone did not improve survival or reversal of shock in patients with septic shock, either overall or in patients who did not have a response to corticotropin, although hydrocortisone hastened reversal of shock in patients in whom shock was reversed. (ClinicalTrials.gov number, NCT00147004.)
AKI - aetiology

- 562 pts with cirrhosis and renal failure (serum creatinine > 1.5 mg/dL (133 micromol/l) on 2 successive determinations within 48 hours)

- Main causes of acute kidney injury in cirrhotic patients

  - infections (213 cases; 46%),

  - hypovolemic-associated renal failure (149; 32%) - diuretics, paracentesis, GI bleed.

  - HRS (60; 13%), and

  - parenchymal nephropathy (41; 9%).

- The remaining patients had a combination of causes or miscellaneous conditions

- Martin-LLahi et al, Gastroenterology 2011:140; 488-496
• If there is tense ascites, the intra-abdominal pressure will approach 20mmHg

• Consider small volume paracentesis (with albumin replacement +/- terlipressin)

• May be sufficient to improve renal perfusion and function
Prognostic Importance of the Cause of Renal Failure in Patients With Cirrhosis

Gastroenterology Volume 140, Issue 2 2011 488 - 496.e4
HRS - pathophysiology/natural history

Obstruction to portal flow

Portal hypertension

Systemic & splanchnic arterial vasodilatation

Activation of vasoconstrictor systems

↑ Renal sensitivity to vasoconstrictors

Renal vasoconstriction

Abnormal renal autoregulation

Cirrhotic cardiomyopathy

HRS II

HRS I

Wong et al, Gut 2011:60:702-709
Dysfunction will also experience adverse outcomes. If so, they should also be offered treatment early rather than waiting until signs of renal failure are fully developed. Indeed, a relative low cardiac output syndrome may therefore be a risk factor for hepatorenal syndrome.

HRS are not an isolated phenomenon, but rather evolve with disease advances. Recognising the inadequacy of serum creatinine as an index of renal dysfunction for possible treatment. Since no studies have been performed in cirrhosis using these proposed definitions, they can best be regarded as expert opinions or level D evidence, and have been shown to predict clinical outcomes with a progressive increase in mortality with worsening RIFLE class.

The high cardiac output state of the hyperdynamic circulation compromises renal perfusion. In cirrhotic patients with ascites, in decompensated cirrhosis means that there is limited cardiac output as liver function is also compromised by correcting for body surface area. The changes that predispose to the development of HRS are not an isolated phenomenon, but rather evolve with disease advances. The patient with cirrhosis is therefore poised to develop renal failure simply because of the presence of cirrhosis was also considered in the RIFLE class, but they represent an important stage renal disease which stratiﬁcation will be validated in prospective trials.

Natural history of cirrhosis: GFR, glomerular filtration rate. Acute kidney injury; GFR, glomerular filtration rate. The use of creatinine clearance in cirrhosis to assess renal function is fraught with problems (Figure 1). The patient with cirrhosis is therefore poised to develop HRS at infection resolution had signiﬁcantly reduced renal blood ow and spontaneous bacterial peritonitis, and therefore further compromises renal perfusion. In cirrhotic patients with ascites, the high cardiac output state of the hyperdynamic circulation compromises renal perfusion. In cirrhotic patients with ascites, the high cardiac output state of the hyperdynamic circulation compromises renal perfusion. In cirrhotic patients with ascites, the high cardiac output state of the hyperdynamic circulation compromises renal perfusion.

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Thus, serum creatinine in patients with cirrhosis is notoriously inaccurate in the diagnosis of renal failure and tubular creatinine secretion compared with renal tubular creatinine secretion compared with renal tubular creatinine secretion. These problems in the estimation of renal function is also unreliable because of the falsely low serum creatinine in these patients coupled with a relatively increased cystatin C kidney injury network (AKIN), an independent collaborative network consisting of experts from ADQI and several nephron segments. Since smaller increases in serum creatinine are not a useful clinical marker of renal dysfunction.

In 2004 the ADQI Working Group developed a consensus deﬁnition of AKI to include an absolute increase in serum creatinine of 0.3 mg/dl (26 µmol/l) when documented to occur within 48 h, which reverses upon decongestion of ascites and spontaneous bacterial peritonitis; this is hepatorenal syndrome Type I (HRS Type I).

In 2002, the IAC Working Group therefore proposed the following deﬁnitions for the diagnosis of renal dysfunction in cirrhosis in order to help identify patients with milder renal dysfunction (Figure 2). It is agreed that AKI will be validated in prospective trials.

The high cardiac output state of the hyperdynamic circulation compromises renal perfusion. In cirrhotic patients with ascites, in decompensated cirrhosis means that there is limited cardiac output as liver function is also compromised by correcting for body surface area. The changes that predispose to the development of HRS are not an isolated phenomenon, but rather evolve with disease advances. Recognising the inadequacy of serum creatinine as an index of renal dysfunction for possible treatment. Since no studies have been performed in cirrhosis using these proposed definitions, they can best be regarded as expert opinions or level D evidence, and have been shown to predict clinical outcomes with a progressive increase in mortality with worsening RIFLE class.

Thus, serum creatinine in patients with cirrhosis is notoriously inaccurate in the diagnosis of renal failure and tubular creatinine secretion compared with renal tubular creatinine secretion. These problems in the estimation of renal function is also unreliable because of the falsely low serum creatinine in these patients coupled with a relatively increased cystatin C.

Wong et al, Gut
2011:60:702-709
AKI - Definitions

• HRS - International Ascites Club definition

  • Cirrhosis with ascites
  • Serum creatinine ≥133 μmol/l (1.5 mg/dl)
  • No improvement in serum creatinine (decrease to a level of ≤133 μmol/l or 1.5 mg/dl) after at least 2 days of diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg body weight/day up to a maximum of 100 g/day
  • Absence of shock
  • No current or recent treatment with nephrotoxic drugs
  • Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhaematuria (>50 red blood cells/high power field) and/or abnormal renal ultrasonography
AKI - Definitions

- HRS - International Ascites Club definition

- Cirrhosis with ascites
- Serum creatinine $\geq 133$ μmol/l (1.5 mg/dl)
- No improvement in serum creatinine (decrease to a level of $\leq 133$ μmol/l or 1.5 mg/dl) after at least 2 days of diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg body weight/day up to a maximum of 100 g/day
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria $>500$ mg/day, microhaematuria ($>50$ red blood cells/high power field) and/or abnormal renal ultrasonography
Type 1 HRS is characterized by a severe and rapidly progressive renal failure, which has been defined as doubling of serum creatinine reaching a level greater than 221 micmol/l (2.5 mg/dL) in less than 2 weeks.

Figure 5. Probability of survival of patients with severe HRS. Reprinted with permission.113
Spectrum of kidney disease in cirrhosis

Wong et al, Gut
2011:60:702-709
# Proposed definition of AKI in cirrhosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney injury</td>
<td>Rise in serum creatinine of ≥50% from baseline or a rise of serum creatinine by ≥26.4 μmol/l (≥0.3 mg/dl) in &lt;48 h</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Glomerular filtration rate of &lt;60 ml/min for &gt;3 months calculated using MDRD6 formula</td>
</tr>
<tr>
<td>Acute-on-chronic kidney disease</td>
<td>Rise in serum creatinine of ≥50% from baseline or a rise of serum creatinine by ≥26.4 μmol/l (≥0.3 mg/dl) in &lt;48 h in a patient with cirrhosis whose glomerular filtration rate is &lt;60 ml/min for &gt;3 months calculated using MDRD6 formula</td>
</tr>
</tbody>
</table>

Wong et al, Gut  
2011:60:702-709
## Proposed definition of AKI in cirrhosis

<table>
<thead>
<tr>
<th>Acute kidney injury</th>
<th>Rise in serum creatinine of ≥50% from baseline or a rise of serum creatinine by ≥26.4 μmol/l (≥0.3 mg/dl) in &lt;48 h HRS type 1 is a specific form of acute kidney injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic kidney disease</td>
<td>Glomerular filtration rate of &lt;60 ml/min for &gt;3 months calculated using MDRD6 formula HRS type 2 is a specific form of chronic kidney disease</td>
</tr>
<tr>
<td>Acute-on-chronic kidney disease</td>
<td>Rise in serum creatinine of ≥50% from baseline or a rise of serum creatinine by ≥26.4 μmol/l (≥0.3 mg/dl) in &lt;48 h in a patient with cirrhosis whose glomerular filtration rate is &lt;60 ml/min for &gt;3 months calculated using MDRD6 formula</td>
</tr>
</tbody>
</table>

Wong et al, Gut 2011:60:702-709
Treatment

• Define the cause - ?parenchymal disease - renal u/s, urinalysis, +/- biopsy

• Treat infection (sepsis may be occult - cultures; hypersplenism may blunt the expected neutrophilia)

• Treat hypovolaemia

• Specific management strategies for HRS

• Ultimately liver transplantation is the best treatment for HRS
HRS - Rx with terlipressin+albumin.
Martin-Llahi et al, Gastroenterology 2008

![Graph showing probability of response over days for treatments terlipressin + albumin and albumin.](https://via.placeholder.com/150)

*Days: 0, 2, 4, 6, 8, 10, 12, 14, 16*

*Probabilities: 0.0, 0.2, 0.4, 0.6, 0.8, 1.0*

*Patients at risk:*
- Terlipressin + albumin: 23, 22, 19, 17, 14, 12, 12, 11, 10
- Albumin: 23, 21, 18, 18, 17, 16, 16, 15, 15

*P < .05*

Terli+alb favours reversal of HRS, improved renal function

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Relative Risk, 95% CI</th>
<th>Relative Risk, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution of Hepatorenal Syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin-Llach 2008</td>
<td>9</td>
<td>23</td>
<td>1</td>
<td>23</td>
<td>13.9%</td>
<td>9.00 [1.24, 66.41]</td>
<td></td>
</tr>
<tr>
<td>Neri 2008</td>
<td>21</td>
<td>26</td>
<td>5</td>
<td>26</td>
<td>38.6%</td>
<td>4.20 [1.87, 9.44]</td>
<td></td>
</tr>
<tr>
<td>Sanyal 2008</td>
<td>19</td>
<td>56</td>
<td>7</td>
<td>56</td>
<td>39.5%</td>
<td>2.71 [1.24, 5.94]</td>
<td></td>
</tr>
<tr>
<td>Solanki 2003</td>
<td>5</td>
<td>12</td>
<td>0</td>
<td>12</td>
<td>7.9%</td>
<td>11.00 [0.67, 179.29]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>117</td>
<td></td>
<td>117</td>
<td></td>
<td>100.0%</td>
<td>3.76 [2.21, 6.39]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>54</td>
<td></td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity I²</td>
<td>0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Improved renal function |                  |       |                |       |        |                        |                        |
| Martin-Llach 2008       | 10               | 23    | 2              | 23    | 17.6%  | 5.00 [1.23, 20.35]     |                        |
| Neri 2008               | 25               | 26    | 16             | 26    | 43.1%  | 1.56 [1.14, 2.14]      |                        |
| Sanyal 2008             | 16               | 56    | 10             | 56    | 33.1%  | 1.60 [0.80, 3.22]      |                        |
| Solanki 2003            | 5                | 12    | 0              | 12    | 6.2%   | 11.00 [0.67, 179.29]   |                        |
| Total (95% CI)          | 117              |       | 117            |       | 100.0% | 2.00 [1.11, 3.62]      |                        |
| Total events            | 56               |       | 28             |       |        |                        |                        |
| Heterogeneity I²        | 47%              |       |                |       |        |                        |                        |
If AKI progresses in cirrhotic patients, what then?

- Renal replacement therapy may be considered in two main groups
  - Bridge to transplant
  - Non-HRS related AKI with a prospect of recovery
- Also used for
  - Management of volume overload in refractory ascites
  - Correction of electrolyte imbalance (sodium - relationship to ICP in ALF, hyper and hyponatraemia predict increased mortality during liver transplantation? causal or associative?)
• Mode of RRT

  • CRRT vs IHD

  • No data as to which is superior - CRRT preferred in ICU due to its haemodynamic stability

• Dose?
## Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators*

### Table: Prespecified Subgroup

<table>
<thead>
<tr>
<th>Prespecified Subgroup</th>
<th>Higher Intensity (N=721)</th>
<th>Lower Intensity (N=743)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with criteria for sepsis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>168/359 (46.8)</td>
<td>186/363 (51.2)</td>
<td>0.84 (0.62–1.12)</td>
</tr>
<tr>
<td>No</td>
<td>154/362 (42.5)</td>
<td>145/379 (38.3)</td>
<td>1.19 (0.89–1.60)</td>
</tr>
<tr>
<td><strong>Patients with at least one nonrenal organ failure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>299/628 (47.6)</td>
<td>306/649 (47.2)</td>
<td>1.02 (0.82–1.27)</td>
</tr>
<tr>
<td>No</td>
<td>23/93 (24.7)</td>
<td>25/93 (26.9)</td>
<td>0.89 (0.46–1.72)</td>
</tr>
<tr>
<td><strong>Patients with SOFA cardiovascular score of 3 or 4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>247/510 (48.4)</td>
<td>254/546 (46.5)</td>
<td>1.08 (0.85–1.37)</td>
</tr>
<tr>
<td>No</td>
<td>74/210 (35.2)</td>
<td>75/194 (38.7)</td>
<td>0.86 (0.58–1.29)</td>
</tr>
<tr>
<td><strong>Patients with eGFR &lt;60 ml/min</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>114/250 (45.6)</td>
<td>105/222 (47.3)</td>
<td>0.93 (0.65–1.34)</td>
</tr>
<tr>
<td>No</td>
<td>81/157 (51.6)</td>
<td>81/185 (43.8)</td>
<td>1.37 (0.89–2.10)</td>
</tr>
<tr>
<td>Missing</td>
<td>127/314 (40.5)</td>
<td>146/336 (43.5)</td>
<td>0.88 (0.65–1.21)</td>
</tr>
<tr>
<td><strong>Death from any cause by day 90</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>322/721 (44.7)</td>
<td>332/743 (44.7)</td>
<td>1.00 (0.81–1.23)</td>
</tr>
</tbody>
</table>
Would a higher dose be of any benefit?

• Optimal clearance of ammonia on CVVHDF at 60 mls/kg
Risks

- CRRT (in common with extracorporeal devices) will result in a fall in platelet count and reduced fibrinogen. This usually does not result in an increased bleeding risk.

- However, patients in liver failure who display evidence of fibrinolysis on thromboelastography may be at increased risk of bleeding when placed on extracorporeal circuits (including MARS).
Severe encephalopathy

- Natural history of chronic liver disease
  - compensated cirrhosis - no encephalopathy, no ascites, +/-varices
    - 5-10% progress annually to
  - decompensated cirrhosis - encephalopathy, ascites, varices, bleeding
    - Outcome - death or transplantation
Figure 2. Kaplan-Meier plot of survival estimates of hospitalized patients with cirrhosis according to grade of hepatic encephalopathy (HE).
**Grades of encephalopathy**

<table>
<thead>
<tr>
<th>HE Grade</th>
<th>Clinical Assessments</th>
<th>Neuropsychological Assessments</th>
<th>HE Grade Determination</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>○ No eyes open</td>
<td>□ Not applicable</td>
<td>All 3 tests impaired</td>
</tr>
<tr>
<td></td>
<td>○ No motor response</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ No verbal response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>○ Somnolence</td>
<td>□ Mental control = 0&lt;sup&gt;26&lt;/sup&gt;</td>
<td>At least 3 tests impaired: clinical or neuropsychological</td>
</tr>
<tr>
<td></td>
<td>○ Confusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Disoriented to place</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Bizarre behavior/ anger/rage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Clonus/rigidity/ nystagmus/Babinsky</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>○ Lethargy</td>
<td>□ Slow responses&lt;sup&gt;26&lt;/sup&gt;</td>
<td>At least 2 clinical and 3 neuropsychological Impaired</td>
</tr>
<tr>
<td></td>
<td>○ Loss of time</td>
<td>□ Anxiety&lt;sup&gt;27&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Slurred speech</td>
<td>□ Amnesia of recent events&lt;sup&gt;28&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Hyperactive reflexes</td>
<td>□ Simple computations&lt;sup&gt;29&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Inappropriate behavior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>○ Sleep disorder</td>
<td>□ Complex computations&lt;sup&gt;29&lt;/sup&gt;</td>
<td>At least 4 tests impaired: clinical or neuropsychological</td>
</tr>
<tr>
<td></td>
<td>○ Tremor</td>
<td>□ Construction ability&lt;sup&gt;30&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Shortened attention span&lt;sup&gt;31&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>□ Depression&lt;sup&gt;27&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>
Risks for developing encephalopathy

- Infection/inflammation
- Bleeding
- Portosystemic shunt
- Acute insult - surgery
- Biochemical disturbances
Treatment

• HE usually not a cause of death in CLF/AoCLF—as long as the airway is managed and resp sepsis prevented

• Treat the precipitant - sepsis, fluids etc

• Standard feed - standard protein, high calorie,fibre content

• Lactulose (non-absorbable disaccharide) remains standard therapy - no mortality benefit - Als-Nielsen, BMJ 2004, 328, 1064

• Rifaxamin - improved maintenance of remission. Bass et al NEJM 2010, 362
Extracorporeal devices for HE?

**A**

![Graph showing mean cumulative number of improvements per person](image)

P < 0.01

**B**

![Graph showing percent with 1st improvement](image)

p=0.045

---

**Randomized Controlled Study of Extracorporeal Albumin Dialysis for Hepatic Encephalopathy in Advanced Cirrhosis**

Tarek I. Hassanein,1 Flemming Tofteng,2 Robert S. Brown, Jr.,3 Brendan McGuire,3 Patrick Lynch,3 Ravindra Mehta,3 Finn S. Larsen,4 Jeff Gornbein,4 Jan Stange,5 and Andres T. Blei6

1. MARS Flux
2. Ion Exchange Resin Column (IE 250)
3. Activated Charcoal Column (AC 250)
4. Conventional Dialysis Column (DiaFlux)
Side effects

<table>
<thead>
<tr>
<th>Complications</th>
<th>Type of Event</th>
<th>Days 1-5</th>
<th>Days 6-10</th>
<th>Days &gt;11-180</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ECAD n = 39</td>
<td>SMT n = 31</td>
<td>ECAD n = 34</td>
<td>SMT n = 26</td>
</tr>
<tr>
<td>Total SAEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 (51%)</td>
<td>8 (26%)</td>
<td>7 (21%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Total death</td>
<td>5 (13%)</td>
<td>5 (16%)</td>
<td>4 (12%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>SAEs possibly related to ECAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SAEs related to catheter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
MARS-RELIEF (2010)

- 189 patients with AOCLF (bilirubin >5 mg/dl and at least one of the following: HE grade II-IV, hepatorenal syndrome or bilirubin >20mg/dl) were randomized either to MARS (n=95) or to standard therapy (ST) (n=94)

- The proportion of patients treated with MARS or ST dying within 28 days was almost identical in the two groups (40.8% vs. 40.0%).

**EXTRACORPOREAL LIVER SUPPORT WITH THE MOLECULAR ADSORBENT RECIRCULATING SYSTEM (MARS) IN PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE (AOCLF). THE RELIEF TRIA**
HELIOS (Prometheus) (2010)

- 145 patients with AOC recruited in 10 centers from 7 European countries were randomized either to standard medical therapy (SMT; n = 68) or to SMT + FPSA therapy (n = 77)

- Extracorporeal liver support therapy by FPSA (Prometheus®) was not associated with an improved survival in all patients with AOC compared to standard medical therapy alone.

- However, a survival advantage was observed in patients with hepatorenal syndrome type I or severe AOC with MELD score >30.
Cardiac dysfunction

Cirrhotic Cardiomyopathy

Enrico M. Zardi, MD,* Antonio Abbate, MD, PhD,‡ Domenico Maria Zardi, MD,§ Aldo Dobrina, MD,§ Domenico Margiotta, MD,* Benjamin W. Van Tassel, PharmD,‡ Antonella Afeletra, MD,* Arun J. Sanyal, MD†
Rome and Trieste, Italy; and Richmond, Virginia

Figure 2 Clinical View on Relationship Between Clinical and Instrumental Abnormalities and Cardiac Function

Progressive deterioration of cardiac function in cirrhosis may be recognized by means of clinical, electrocardiographic (ECG), and echocardiographic abnormalities whose severity is predictive of contemporary seriousness of heart failure. CO = cardiac output.
Acute Liver failure

• Acute liver failure (ALF) is a rare condition in which rapid deterioration of liver function results in altered mentation and coagulopathy in individuals without known pre-existing liver disease

• INR >1.5, and any degree of mental alteration (encephalopathy) in a patient without preexisting cirrhosis and with an illness of <26 weeks’ duration

• causes

  • drug-induced liver injury, viral hepatitis, autoimmune liver disease and

  • shock or hypoperfusion;

  • many cases (c.15%) have no discernible cause.
Prior to transplantation, most series suggested less than 15% survival.

Currently, overall short-term survival (one year) including those undergoing transplantation is greater than 65%.
Cerebral Edema/Intracranial Hypertension

Grade I/II Encephalopathy
Consider transfer to liver transplant facility and listing for transplantation
Brain CT: rule out other causes of decreased mental status; little utility to identify cerebral edema
Avoid stimulation; avoid sedation if possible
Antibiotics: surveillance and treatment of infection required; prophylaxis possibly helpful
Lactulose, possibly helpful
Grade III/IV Encephalopathy

Continue management strategies listed above
Intubate trachea (may require sedation)
Elevate head of bed
Consider placement of ICP monitoring device
Immediate treatment of seizures required; prophylaxis of unclear value
Mannitol: use for severe elevation of ICP or first clinical signs of herniation
Hypertonic saline to raise serum sodium to 145-155 mmol/L
Hyperventilation: effects short-lived; may use for impending herniation
Infection

Surveillance for and prompt antimicrobial treatment of infection required
Antibiotic prophylaxis possibly helpful but not proven

Coagulopathy

Vitamin K: give at least one dose
FFP: give only for invasive procedures or active bleeding
Platelets: give only for invasive procedures or active bleeding
Recombinant activated factor VII: possibly effective for invasive procedures
Prophylaxis for stress ulceration: give H$_2$ blocker or PPI
Hemodynamics/Renal Failure

Volume replacement
Pressor support (dopamine, epinephrine, norepinephrine) as needed to maintain adequate mean arterial pressure
Avoid nephrotoxic agents
Continuous modes of hemodialysis if needed
Vasopressin recommended in hypotension refractory to volume resuscitation and no epinephrine
Metabolic Concerns

Follow closely: glucose, potassium, magnesium, phosphate
Consider nutrition: enteral feedings if possible or total parenteral nutrition
Who needs a transplant?

King’s College Criteria

Acetaminophen-Induced ALF
- Strongly consider OLT listing if:
  - arterial lactate $\geq 3.5$ mmol/L after early fluid resuscitation
- List for OLT if:
  - pH $< 7.3$ - or -
  - arterial lactate $\geq 3.0$ mmol/L after adequate fluid resuscitation
- List for OLT if all 3 occur within a 24-hour period:
  - presence of grade 3 or 4 hepatic encephalopathy
  - INR $\geq 6.5$
  - Creatinine $\geq 3.4$ mg/dL
Non-Acetaminophen-Induced ALF

- List for OLT if:
  - INR > 6.5 and encephalopathy present (irrespective of grade)
  or any three of the following (encephalopathy present; irrespective of grade):
  - Age < 10 or > 40 years‡
  - Jaundice for > 7 days before development of encephalopathy‡
  - INR ≥ 3.5
  - serum bilirubin ≥ 17 mg/dL
  - Unfavorable etiology, such as
    Wilson Disease
    idiosyncratic drug reaction
    seronegative hepatitis
Conclusion

• Identify priorities in management based on presentation (CLF/AoCLF; ALF)

• Trial of therapy in cirrhotic patients (outcome in MOF remains poor)

• Specific Rxs for GI bleed, HRS, hepatic encephalopathy

• Is liver able to regenerate or is transplantation an option?