Management of the Cirrhotic Patient in the ICU

Peter E. Morris, MD
Professor & Chief,
Pulmonary, Critical Care and Sleep Medicine
University of Kentucky
Conflict of Interest

• Funding
  US National Institutes of Health
    National Heart, Lung Blood Institute (NHLBI)
    National Institute of Nursing Research (NINR)
  US Department of Defense (DOD)
Educational Need/Practice Gap

Gap =
• Highlight where our literature now stands
• Discuss where our practice does and does not reflect the literature
• Create a discussion for direction of needed new clinical trials

Need =
Literature regarding the ICU Management of the Decompensated Cirrhotic patient is in need of robust, large, multicenter clinical trials
Objectives

Upon completion of this educational activity, you will be able to:

• Describe the limitations of current medical literature surrounding the critically ill, decompensated cirrhosis patient

• Discuss the limitations of current literature and how the limitations drives future clinical trail designs
Controversy Exists!
Call Attention to Bias in the Medical Literature

- Critical Care Multicenter trials – typically exclude cancer patients and decompensated cirrhosis patients
Bias within the Critical Care Clinical Trial Community

- Liver disease is a common exclusion from mainstream critical care trials
- Often, we do not know beyond empiricism what is best ICU care for failing liver in patients with cirrhosis
- Examples of exclusions
Unadjusted 90-day mortality was 23.6% in the prone group; 41% in control, p <0.001
Exclusions

• severe chronic liver disease (Child–Pugh class C) (82 patients, 8.3%),

• bone marrow transplantation or chemotherapy-induced neutropenia (97 patients, 9.8%),
Arguments for Funding

• Large scale, network-level interventional studies
• Quicker turn-around time – large numbers of patients
Important Terminology

- “Functional Recovery”
Experiencing a Critical Illness Appreciation of Functional Trajectory

12 mo prior to ICU admission

Hospitalization with ICU stay

12 mo post ICU admission
Management of the Decompensation and its Consequences

- **Cardiovascular** - high cardiac output with low systemic vascular resistance and decreased arterial blood pressure
- **Hepatic encephalopathy** may often be exacerbated by infections and electrolyte abnormalities which are often present in the critically ill
- **Pulmonary** – pneumonia, Acute Lung Injury, Hepatic Hydrothorax, Portopulmonary HTN
- **Hematologic** – thrombocytopenia and decreased clotting factors
- **Renal** – Hepatorenal syndrome and Acute Kidney Injury
Acute on Chronic Liver Failure (ACLF)

- ACLF typically progresses in patients with cirrhosis undergoing acute decompensation with ascites, jaundice, variceal hemorrhage, encephalopathy, and bacterial infections.
What is the appropriate $1^0$ outcome in critical care trials with Decompensated Cirrhosis Patients?

- Off ventilator?
- Reversal of shock?
- Improvement of creatinine?
- Discharge from the ICU?
What is the appropriate outcome in critical care trials

- 3 month survival
- 6 month survival
- 12 month survival
- Functional outcomes
- Functional trajectories
Management

• Even patients with well compensated cirrhosis may suffer acute deterioration, the syndrome of acute-on-chronic liver failure (ACLF) results in multi-system organ dysfunction marked increase in associated short-term morbidity and mortality
Cardiovascular Management

• Portal hypertension induces progressive systemic and splanchnic vasodilatation leads to an initial *hyperdynamic* state

• Initially, the *hyperdynamic* circulatory state includes:
  – high cardiac output
  – low systemic vascular resistance
  – decreased arterial blood pressure
Recognition of Frailty
Cardiovascular Management

• Total blood & plasma volume is increased:
  – “effective” central blood volume is decreased due to pooling within the splanchnic vascular bed

• Low effective circulating volume results in activation of the neurohormonal axis =
  – sodium and water retention
  – increases in heart rate

• In compensated stable patients, compensatory mechanisms maintain end-organ perfusion

• However, even small perturbations in this system may result in significant hypotension.
Cardiovascular Management

• Push – Pull relationship between Diuretic Therapy & Pressor Therapy
Pulmonary Oxygen & Ventilator Support

- Acute respiratory failure, e.g. pneumonia, acute lung injury, or hepatic hydrothorax
- Respiratory complications hampered by:
  - portopulmonary hypertension
  - hepatopulmonary syndrome
In the background – a huge complication of cirrhosis lurks----

• Hepatopulmonary syndrome - Parenchymal *Shunt*

• Complicates ability to oxygenate
• Lowers threshold of intubation
• Less resilience to withstand any systemic inflammation’s effect on lung
Encephalopathy in Decompensated Cirrhosis Patients

• Fix the primary syndrome
• In patients who fail to respond to lactulose or other therapies, or in patients whose HE onset is particularly **abrupt** or severe = brain imaging & EEG
• Ammonia Levels- controversial – newer approach baseline Ammonia – (normal levels help exclude)
• But not to perform routine measurement of ammonia levels in critically ill patients with cirrhosis – treat to clinical endpoints (patient exam)
Hepatic Encephalopathy (HE)

• Intubation for Glasgow coma score of $\leq 8$ = airway protection
• Intubated patients - limit sedative meds
• Usage of short acting agents: fentanyl +/- propofol

• Avoidance of benzodiazepines is recommended
Rifaximin

- Rifaximin, a minimally absorbed antibiotic
- A RCT lactulose alone vs lactulose plus rifaximin decrease mortality (23.8% vs. 49.1%, P<0.05) decrease in length of stay (5.8 vs 8.2 d)
- Practice has moved to use rifaximin in HE dosed at 550 mg BID

Hematologic

- Risk of Bleeding not upheld by literature
- Field – becoming more comfortable with bedside procedures despite low platelets & elevated INR

  [avoidance of blood products]

- Field – moving toward DVT prophylaxis despite low platelets and elevated INR – still risk of new venous thrombosis
Infectious Complications

• The prevalence of multidrug-resistant bacteria is high in this population
• Initial approach to decompensation = broad spectrum antibiotics should be initiated as soon as infection is suspected
Renal Controversies Abound in Acute on Chronic Liver Failure (ACLF)
Hepatorenal Syndrome vs AKI

• Management controversies abound
• Differentiating the two dx’s
• Should a pressor agent be applied – if so does it matter which one?
• Should Albumin be applied? Endpoint?
• Justification Data for albumin – large, well controlled studies are lacking
Tension between ICU Rationalists and ICU Empiricists

• Rationalists:
  – 2C recommendation is not a “green light” to apply a therapy \{Harm\}

• Empiricists:
  – “If I had to publish all the care I provide, I would never get anything done!”
  – “I’ve seen it work”
“There is nothing that ruins a good argument like good data”

Roger DePrez, MD
1988
Current status

• Empiricism
• Overstating the available data with bias
• Example from a leading review,
  • “Albumin has proven benefit in certain clinical situations including spontaneous bacterial peritonitis, after large volume paracentesis, and in type-1 hepatorenal syndrome (10).”


The Plea for Increased Funding for RCTs in Acute on Chronic Liver Failure

• Current literature ACLF - HRS & ACLF - AKI
  – Heterogeneous populations in same study
  – Small numbers/single center
  – Variability in or lack of a control arm
Current Recs

• In practice Approach is Varied; titration & endpoints of Rx unclear (creatinine decrease, urine output, MAP)

• HRS –
  – Splanchnic vasodilatation
  – local increases in renal vascular resistance (that result in part from hypotension-induced activation of the renin-angiotensin/sympathetic nervous system)
  – volume expansion - albumin
  – Rx splanchnic vasodilatation – pressor agent
Meta-Analyses

• comprehensive assessment of the body of available knowledge
There are many Meta-Analyses

• The good and the bad –
• When small studies are included – if a positive outcome is identified – what does it suggest as next steps?

• **Question** – *implement into practice?*
• **Justification to Design a larger study?**
• Message from HRS Meta-analyses
  – *median study arm contain 24 patients*,
    include prospective uncontrolled (no control arm) and mixed diagnoses
  – Potential for Bias
Limitation of Small Numbers of Trial Study Patients with Critical Illnesses

• Too much heterogeneity already exists for critical illness –
  – duration, comorbidities, resuscitation timelines –
    even with robust inclusion exclusion criteria –
    small numbers are considered a limitation for bias

• Example: NIH PETAL Network’s study
  – Reevaluation Of Systemic Early neuromuscular blockade (ROSE) –
    will enroll >1400 patients (700+ to one of 2 arms)
Justification of Increased Federal Funding
ACLF & ICU Outcomes

• Meta-analyses from 13 outcome studies (2523 cirrhotic patients)
• In-ICU, in-hospital, and 6-month mortality was 42.7, 54.1, and 75.1%, respectively

Future

- Appreciation of “delicate” baseline organ function (lung, kidney)
- Earlier monitoring
- Less blood product exposure
- Broad spectrum antibiotics early for organ dysfunction
- Plea for Federal Funding of Multicenter RCTs for interventions