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**Disclosures**

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*Dr. Shingina has no relevant financial relationships with ineligible companies.*

Robert J. Wong, MD, MS, FACG

*Gilead Sciences (institutional research grant)*

*Exact Sciences (institutional research grant)*

*Thera Technologies (institutional research grant)*

*All of the relevant financial relationships listed for these individuals have been mitigated*
American College of Gastroenterology
Acute Liver Failure Guidelines

Alexandra Shingina, MD, MSc, Nizar Mukhtar, MD, Jamile Wakim-Fleming, MD, FACG, Saleh Alqahtani, MBCR, MS, Robert J. Wong, MD, MS, FACG, Berkeley N. Limketkai, MD, PhD, FACG, Anne M. Larson, MD and Lafaine Grant, MD

Email: Alexandra.Shingina@vumc.org
@ASHinginaMD
Objectives

- To review the literature published on the topic
  - Using PICO questions
- To come up with evidence-based recommendations on diagnosis and management of ALF aimed at general gastroenterologist
- Recommendations
  - Using GRADE assessment tool
- Key Concepts
  - Statements to which GRADE process can not be applied
  - Definitions and epidemiological statements

ALF Definitions

- Acute Liver Failure (ALF)
  - Liver injury (abnormal LFTs) AND
  - Coagulopathy (INR>1.5) AND
  - Hepatic Encephalopathy
- Severe Acute Liver Injury
  - INR>2 and bilirubin>3mg/dl
  - No Hepatic Encephalopathy
- Annual incidence 2000-4000 cases/year
- Acute Liver Failure Study Group (ALFSG)
  - 2614 ALF and 857 ALI adults

Wilson’s disease, Budd-Chiari and ALF can have ACLF presentation but can still be considered ALF.
ALF Etiology

A. Aetiology ALF (n=314)

B. Aetiology PALF (n=149)

Europe

USA

ALF presentation

Table 4. ALF presentations

<table>
<thead>
<tr>
<th>Type of ALF</th>
<th>Time frame</th>
<th>Examples</th>
<th>Risk of cerebral edema</th>
<th>Risk of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hypereutopic</td>
<td>&lt;7 d</td>
<td>Acetaminophen hepatitis A &amp; E ischemic injury</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Acute</td>
<td>7–21 d</td>
<td>Hepatitis B</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Subacute</td>
<td>&gt;21 d and &lt;26 wk</td>
<td>Nonacetaminophen DILI</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>ALF</td>
<td>acute liver failure; DILI, drug-induced liver injury</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ALF presentation

To biopsy or not?

**Pros**
- Can help to rule out infiltrative malignancy
- Can help diagnose ACLF
- Can help identify infections
- Can help in diagnosis of AIH

**Cons**
- Fear of bleeding in the setting of coagulopathy
- Fear of complications
ALF: Liver Biopsy

• Key Recommendations
  • Liver biopsy may help exclude infiltrative disease and malignancy and to identify patients with contraindication to LT.
  
  • Liver biopsy may help diagnose AIH, which may respond to immunosuppressive therapy and potentially spare patients the long-term complications of LT.
  
  • There is insufficient evidence to recommend the routine use of liver biopsy in other settings.
  
  • When considering liver biopsy in the evaluation of patients with ALF, we suggest using TJLB over other methods.

ALF Work up

• History, history, history
  • Exposures
  • Medication reviews
  • Collateral

• Consult to GI/Hepatology

<table>
<thead>
<tr>
<th>Laboratory analysis</th>
<th>Imaging</th>
<th>Consultations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td>N/A</td>
<td>Hepatology</td>
</tr>
<tr>
<td>CT</td>
<td>N/A</td>
<td>Gastroenterology</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>N/A</td>
<td>ICU</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>N/A</td>
<td>Contact transplant center</td>
</tr>
</tbody>
</table>

Table 8. Initial diagnostic workup

- Shingina et al., AJG, 2023
Management: CNS

![Graph showing arterial ammonia concentration](image)

**Fig. 1.** Arterial plasma ammonia concentration in 30 patients who did not develop cerebral herniation (No CH) and 16 patients who died from cerebral herniation (CH). The error bars in the left of each group are median (interquartile range). *P* = 0.001. □ patients who died from other reasons (n = 3).

**Fig. 3.** Changes in arterial ammonia concentration after 1 and 24 h after the initiation of continuous veno-venous hemofiltration. Arterial ammonia reported as median (interquartile range) concentration.

<table>
<thead>
<tr>
<th>Ammonia (μmol/L)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>77%</td>
<td>55%</td>
</tr>
<tr>
<td>150</td>
<td>58%</td>
<td>76%</td>
</tr>
<tr>
<td>200</td>
<td>42%</td>
<td>87%</td>
</tr>
</tbody>
</table>

CCardoso et al., Hepatology, 2018
Management: CNS Hypothermia

- SR and MA of Hypothermia use in ALF
  - Mean targets increasing by 2°C in the latest trials compared with 20 years ago (from means of 32°C to 34°C)
  - Overall, the survival rates between TTM and normothermic groups are similar (63% vs 60%, respectively).

Management: CNS ICP Monitors

<table>
<thead>
<tr>
<th>Year of publication</th>
<th>Author</th>
<th>Single or multi-center</th>
<th>Number of patients</th>
<th>Type of invasive monitor used</th>
<th>Cerebral pathology reversal strategy</th>
<th>Consistent use of a single protocol?</th>
<th>Post-procedure imaging required in all patients?</th>
<th>Incidence of intracranial hemorrhage</th>
<th>Incidence of elevated ICP</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>Kaur et al.</td>
<td>Single-center</td>
<td>14 children</td>
<td>Intracerebral 100%</td>
<td>rFF/ia plus ICP within 30 min prior to procedure to achieve INR &lt;1.5; rFFa 5%</td>
<td>Yes</td>
<td>Not reported</td>
<td>Symptomatic 7%</td>
<td>Not reported</td>
</tr>
<tr>
<td>2014</td>
<td>Mardelis et al.</td>
<td>Multi-center (ALFSC)</td>
<td>140</td>
<td>Subdural 17%; Intracerebral 24%; epidural 23%; lumbar 17%; external ventricular drain 9%</td>
<td>FFP 9%; plasma transfusions in 41%; rFFa 5%</td>
<td>No</td>
<td>No</td>
<td>Symptomatic 7%</td>
<td>51%</td>
</tr>
<tr>
<td>2016</td>
<td>Maloney et al.</td>
<td>Single-center</td>
<td>20</td>
<td>Intracerebral 65%; epidural 35%</td>
<td>FFP and rFFa to goal INR &lt;1.5; platelet transfusions to goal 50,000/µL</td>
<td>Not reported</td>
<td>No</td>
<td>Overall 15% reported, Intracerebral 2 of 10 (20%) with imaging available (both total); epidural 1 of 1 (10%) with imaging available (pentaprobes)</td>
<td>78%</td>
</tr>
<tr>
<td>2016</td>
<td>Bernal et al.</td>
<td>Multi-center clinical trial of hypothermia in ALF</td>
<td>43</td>
<td>Intracerebral 100%</td>
<td>Not reported</td>
<td>Not reported</td>
<td>No</td>
<td>None - one episode hemorrhage to the temporal lobe</td>
<td>49%</td>
</tr>
<tr>
<td>Current study</td>
<td>Rajasek et al.</td>
<td>Single-center</td>
<td>24</td>
<td>Intracerebral 100%</td>
<td>See Table 1</td>
<td>Yes</td>
<td>Yes</td>
<td>4% (symptomatic 4%)</td>
<td>54%</td>
</tr>
</tbody>
</table>

Ribaud et al., Nurs in Crit Care, 2023
Rajasek et al., Crit Care, 2018
Management: CNS Recommendations

• **Key concepts**
  • Patients with ALF with grade 2 or higher encephalopathy should be monitored in an ICU setting.
  • Patients with ALF with grade 3 and 4 encephalopathy should be intubated for airway protection.
  • There is no conclusive evidence to recommend for or against the use of lactulose or rifaximin for the treatment of encephalopathy in patients with ALF.
  • There is no conclusive evidence to recommend routine ICP monitor placement in patients with ALF.
  • There is no conclusive evidence to recommend routine use of hypothermia to control ICP in patients with ALF.

• **Recommendation**
  • In patients with ALF and grade 2 or higher encephalopathy, we suggest early CRRT for the management of hyperammonemia even in the absence of conventional RRT indications.
  
  **GRADE recommendation: conditional, very low quality of evidence.**

Shingina et al., AJG, 2023

Management: Coagulopathy

• Rebalanced state of hemostasis
• Significant bleeding is rare (<5%)
• Viscoelastic testing (ex. TEG)
• Stravitz et al., Hepatology 2021
  • 200 patients with ALI and ALF
Management: CNS Recommendations

- **Key concepts**
  - The INR does not accurately reflect bleeding risk in patients with ALF.
  - Viscoelastic tests may provide a more accurate assessment of coagulopathy in patients with ALF.

- **Recommendation**
  - In patients with ALF, in the absence of active bleeding or impending high-risk procedure, we recommend against routine correction of coagulopathy.
  
  **GRADE recommendation: conditional, very low quality of evidence.**

Management: Infection

- ALF patients have high incidence of infection
  - Up to 1/3 is fungal infection
  - Up to 1/3 have no fever or leukocytosis

- Procalcitonin failed to differentiate infected from non-infected ALF patients

---

Rolando et al., Hepatology, 1990
Rule et al., Plos One, 2015
Karvellas et al., Clin Gastro Hep, 2014
Management: Infection Recommendations

• **Key concepts**
  - In ALF patients, early assessment for infection is prudent as clinical signs of infection are frequently absent.
  - There is insufficient evidence in ALF patients to recommend the use of procalcitonin as a biomarker of infection.
  - Empiric antibiotic and antifungal therapy may be considered in the setting of clinical deterioration of the patient.
  - In patients with ALF, we suggest regular surveillance cultures, however the optimal frequency is unknown.

• **Recommendation**
  - In patients with ALF, we recommend against the routine use of prophylactic antimicrobial agents given no improvement in either rate of bloodstream infection or 21-day mortality. *GRADE recommendation: conditional, low quality of evidence.*

Management: Hemodynamics and Renal Failure

• Similar to septic shock
  - High cardiac output
  - Low systemic vascular resistance
  - Decreased effective circulating volume

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Norepinephrine</th>
<th>Dopamine</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-A vs. W-B (95% CI)</th>
<th>Risk Ratio M-A vs. V-B (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clas et al.</td>
<td>7</td>
<td>1</td>
<td>8</td>
<td>1.26</td>
<td>0.00 (0.00, 1.00)</td>
<td>0.00 (0.00, 1.00)</td>
</tr>
<tr>
<td>De Bonte et al.</td>
<td>14</td>
<td>1</td>
<td>15</td>
<td>3.73</td>
<td>0.00 (0.00, 1.00)</td>
<td>0.00 (0.00, 1.00)</td>
</tr>
<tr>
<td>De Bonte et al.</td>
<td>20</td>
<td>1</td>
<td>21</td>
<td>3.73</td>
<td>0.00 (0.00, 1.00)</td>
<td>0.00 (0.00, 1.00)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>33</td>
<td>1</td>
<td>34</td>
<td>5.50</td>
<td>0.00 (0.00, 1.00)</td>
<td>0.00 (0.00, 1.00)</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>2</td>
<td>62</td>
<td>7.23</td>
<td>0.00 (0.00, 1.00)</td>
<td>0.00 (0.00, 1.00)</td>
</tr>
</tbody>
</table>

Norepinephrine vs. dopamine 28d mortality

*Abri et al., Plos One, 2015*
Management: Hemodynamics and Renal Failure

Key concepts
- In patients with ALF and hypotension, IV fluid resuscitation should be initiated.
- RRT should be considered early in patients with acute kidney injury, electrolyte or metabolic abnormalities, and/or volume overload.
- In patients with ALF requiring RRT, we recommend CRRT over intermittent hemodialysis.

Recommendations
- In patients with ALF, we recommend norepinephrine as the first-line vasopressor for hypotension refractory to fluid resuscitation. **GRADE recommendation: strong, moderate quality of evidence.**
- In patients with ALF with hypotension not responsive to norepinephrine, we suggest adding vasopressin as a secondary agent. **GRADE recommendation: conditional, low quality of evidence.**

Management: DILI

- Idiosyncratic DILI
  - Not dose dependent
  - Variable latency
  - Antimicrobials followed by CAM
  - Subacute DILI has less favorable prognosis
Management: DILI

**Key concepts**
- In patients with APAP-ALI or APAP-ALF, the duration of NAC treatment should be individualized based on the patient's clinical condition and laboratory values.
- In patients with APAP overdose, we recommend single-dose activated charcoal administration if ingestion is known to have occurred within 4 hours.

**Recommendations**
- In patients with non-APAP ALF, we suggest the initiation of intravenous NAC.
  
  **GRADE recommendation: strong, moderate quality of evidence**

---

Management: Hemodynamics and Renal Failure

**Key concepts**
- In patients with APAP-ALI or APAP-ALF, the duration of NAC treatment should be individualized based on the patient's clinical condition and laboratory values.
- In patients with APAP overdose, we recommend single-dose activated charcoal administration if ingestion is known to have occurred within 4 hours.

**Recommendations**
- In patients with non-APAP ALF, we suggest the initiation of intravenous NAC.
Management: AIH

- Acute severe AIH
  - Jaundice
  - No cirrhosis
  - INR>1.5
  - Symptom onset <26 weeks
  - ALF in 3-6%
  - Overlap with
    - ACLF
    - immune-mediated DILI
    - DILI-induced AIH

Stravitz et al., Hepatology, 2023
Rahim et al., LTx, 2019

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of pts</th>
<th>Steroid dose</th>
<th>Groups</th>
<th>Outcome</th>
<th>Misc</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Martin, J Hep, 2021</td>
<td>128 pts with AS-AIH</td>
<td>Dose at the discretion of investigator (1mg/kg)</td>
<td>90% received steroids</td>
<td>Overall survival 88%</td>
<td>SURFASA score</td>
</tr>
<tr>
<td>Kalliopi, Hep Res, 2019</td>
<td>184 AS-AIH</td>
<td>Methylpred 1g qd x3 or IV prednisolone 1mg/kg/day</td>
<td>34 received steroids</td>
<td>Complete response more often in treated vs non treated groups</td>
<td></td>
</tr>
<tr>
<td>Yeoman, J Hep, 2014</td>
<td>32 pts with AS-AIH</td>
<td>Either oral prednisolone or intravenous hydrocortisone (median dose 40 mg/day and 300 mg/day, respectively)</td>
<td>23 received steroids</td>
<td>Untreated group required LT more often</td>
<td>60% required LT, 20% died</td>
</tr>
<tr>
<td>Yeoman, Hep, 2011</td>
<td>72 pts with AS-AIH</td>
<td>Prednisolone at a dose of 40-60 mg/day</td>
<td>All treated</td>
<td>Untreated group had higher mortality</td>
<td>Treatment failure in 18%</td>
</tr>
</tbody>
</table>

Rahim et al., LTx, 2019
Management: Hemodynamics and Renal Failure

**Key concepts**

- In patients presenting with AS-AIH, we recommend the use of IV corticosteroids.
- In patients with AS-AIH that has progressed to ALF, we recommend early evaluation for LT.

Liver Transplant Considerations: KCC

- Development of HE -> transfer to transplant center
- **KCC**
  - Non-APAP induced ALF
    - Sensitivity 68%
    - Specificity 82%
  - APAP induced ALF
    - Sensitivity 65%
    - Specificity 93%

<table>
<thead>
<tr>
<th>Table 11: Prognostic models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic model</td>
</tr>
<tr>
<td>MELD score</td>
</tr>
<tr>
<td>King’s College Criteria</td>
</tr>
<tr>
<td>Child-Pugh</td>
</tr>
<tr>
<td>DeCoule Criteria</td>
</tr>
</tbody>
</table>

Shingina et al., AJG, 2023
Liver Transplant Considerations: KCC

King College Criteria Systematic Reviews

Liver Transplant Considerations: MELD

Table 2. Individual and Pooled Sensitivity, Specificity, and AUC for KCC and MELD

<table>
<thead>
<tr>
<th>Study</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC for KCC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC for MELD</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCC</td>
<td></td>
<td></td>
<td></td>
<td>MELD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC 0.76</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Craig et al., Alim Pharm and Ther, 2010
McPhail et al., J Hep, 2010

McPhail et al., Clin Gastro Hep, 2016
Liver Transplant Consideration

Key concepts
• Identifying patients with ALF at risk of poor outcomes is important and should trigger transfer to a transplant center early in presentation.

Recommendations
• In patients with ALF, we recommend using either the KCC or MELD score for prognostication. Patients meeting the KCC criteria or presenting with MELD >25 are at high risk of poor outcomes. GRADE recommendation: conditional, low quality of evidence.

Shingina et al., AJG, 2023

Evaluation Timeline

- ED Presentation
- ICU Transfer
- Transfer to transplant center
- Transplant Ineligible or Improvement

First 2-4 hours
- Initial Stabilization
- Initial Investigations (Table 5)
- Consider transfer to ICU if HE
- Contact Transplant Center

First 4-12 hours
- Consult psychiatry/social work/hepatobiliary surgery to determine transplant eligibility
- Intensive monitoring
  • Q6hrs CMP/JNR, PO4
  • Q1hr glucose and neuro check
  • Cerebral edema precautions (See text)
- A Transplant eligible, listing

Supportive Management

American College of Gastroenterology
Liver Transplant Consideration

- Graft considerations
  - 18.2% of patients die or become too sick for LT
  - LDLT
    - SR and MA showed no difference in survival
      - 3 studies, 2533 adult patients, 155 LDLT
  - ABO-I
    - With non-A2 grafts
    - No ALF specific literature

Management: Transplant Considerations

Key concepts
- Identifying patients with ALF at risk of poor outcomes is important and should trigger transfer to a transplant center early in presentation.
- Multidisciplinary discussion involving the transplant team to determine individual transplant candidacy should be undertaken at the transplant center.
- In patients with ALF, listed as status 1A priority, LDLT may be considered in centers with LDLT experience when DDLT is not readily available.
- In patients with ALF, listed as status 1A priority, we suggest consideration of ABO-I grafts in a rapidly declining patient.
Questions

Alexandra Shingina, MD, MSc

Robert J. Wong, MD, MS, FACP