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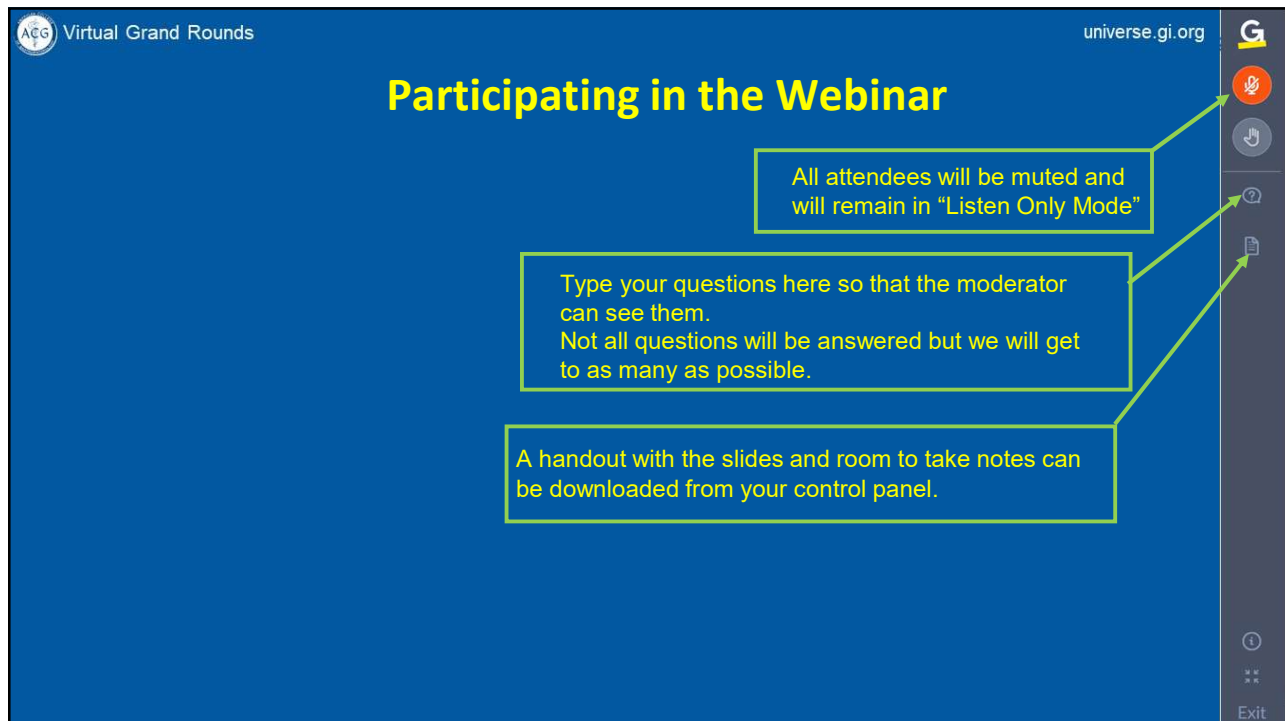
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Alexandra Shingina, MD, MSc  
*Dr. Shingina has no relevant financial relationships with ineligible companies.*



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**AJG** The American Journal of  
GASTROENTEROLOGY

# American College of Gastroenterology Acute Liver Failure Guidelines



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## Authors

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## 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

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## ALF Definitions

- Acute Liver Failure (ALF)
  - Liver injury (abnormal LFTs) AND  New, <26 weeks of onset
  - Coagulopathy (INR>1.5) AND
  - Hepatic Encephalopathy
- Severe Acute Liver Injury
  - INR>2 and bilirubin>3mg/dl
  - No Hepatic Encephalopathy
- Annual incidence 2000-4000cases/year
- Acute Liver Failure Study Group (ALFSG)
  - 2614ALF and 857ALI adults

Wilson's disease, Budd-Chiari and ALF can have ACLF presentation but can **still** be considered ALF

Shingina et al., AJG, 2023  
 Lenz et al., JPGN, 2023  
 Stravitz et al., Hepatology, 2023

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# ALF Etiology

|  | Acetaminophen (n=1261) | Ischemic (n=221) | Drug-induced Liver Injury (n=284) | Autoimmune Hepatitis (n=193) | Hepatitis B virus (n=187) | Hepatitis A virus (n=41) | Pregnancy (n=39) | All other causes (n=405) |
|--|------------------------|------------------|-----------------------------------|------------------------------|---------------------------|--------------------------|------------------|--------------------------|
| Age (median, years)                          | 37                     | 53               | 46                                | 44                           | 45                        | 50                       | 30               | 43                       |
| Women (%)                                    | 75%                    | 58%              | 69%                               | 77%                          | 47%                       | 49%                      | 100%             | 61%                      |
| Jaundice to coma (median, days)              | 1                      | 2                | 13                                | 15                           | 8                         | 4                        | 6                | 9                        |
| Hepatic encephalopathy grade 3 or higher (%) | 50%                    | 55%              | 32%                               | 28%                          | 49%                       | 54%                      | 54%              | 38%                      |
| Alanine aminotransferase (median, IU/L)      | 3779                   | 2334             | 635                               | 449                          | 1402                      | 2229                     | 60               | 582                      |
| Bilirubin (median, mg/dL)                    | 4.3                    | 3.8              | 21.6                              | 22.8                         | 19.9                      | 12.0                     | 11.2             | 18.6                     |
| Listed for Transplant* (%)                   | 23%                    | 5%               | 56%                               | 60%                          | 56%                       | 59%                      | 33%              | 48%                      |
| Transplanted* (%)                            | 9%                     | 3%               | 41%                               | 59%                          | 40%                       | 32%                      | 18%              | 35%                      |
| Transplant-free survival* (%)                | 69%                    | 67%              | 31%                               | 17%                          | 24%                       | 59%                      | 67%              | 23%                      |
| Overall survival* (%)                        | 77%                    | 68%              | 70%                               | 71%                          | 59%                       | 88%                      | 82%              | 56%                      |

Data were collected between Jan 1, 1998 and Dec 2, 2022. Total number of ALF patients=2631. \*Represents outcomes 21 days after admission to Acute Liver Failure Study Group Registry.

**USA**

**A Aetiology ALF (n=314)**

**B Aetiology PALF (n=149)**

**Europe**

Lenz et al., 2023, JPGN  
Stravitz et al., Hepatology, 2023

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# ALF presentation

| Table 4. ALF presentations |                  |  |                        |               |
|----------------------------|------------------|--|------------------------|---------------|
| Type of ALF                | Time frame       | Examples   | Risk of cerebral edema | Risk of death |
| Hyperacute                 | <7 d             | Acetaminophen hepatitis A & E<br>ischemic injury | High                   | Low           |
| Acute                      | 7–21 d           | Hepatitis B                                      | Intermediate           | Intermediate  |
| Subacute                   | >21 d and <26 wk | Nonacetaminophen DILI                            | Low                    | High          |

ALF, acute liver failure; DILI, drug-induced liver injury.

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## ALF presentation

**Table 6. Differences between ALF and ACLF**

|                                      | ALF  | ACLF  |
|--------------------------------------|--|---|
| Age                                  | Younger  | Older   |
| Chronic liver disease                | Absent   | Present<br>Signs of portal hypertension                         |
| Precipitating factors (by frequency) | DILI, viral hepatitis, autoimmune hepatitis              | Infection, alcohol, GI bleeding,                                |
| Clinical signs                       | Liver injury, INR > 1.5, HE                              | Coagulopathy, elevated bilirubin, shock, multiorgan dysfunction |
| Liver biopsy                         | Necrosis and collapse                                    | Fibrosis  |
| CNS                                  | Increased intracranial pressure<br>Use CRRT early for HE | HE responds to lactulose/Rifaximin                              |
| Infection                            | Late (<5 d)  | Early (<5 d)  |
| Renal failure                        | Hypoperfusion, ATN                                       | HRS-AKI   |
| Respiratory                          | ARDS rare  | ARDS common   |
| Liver transplantation                | KCC, MELD<br>Status 1A listing                           | MELD<br>No priority in MELD system                              |

ACLF, acute on chronic liver failure; ALF, acute liver failure; ARDS, acute respiratory distress syndrome; ATN, acute tubular necrosis; CNS, central nervous system; CRRT, continuous renal replacement therapy; DILI, drug-induced liver injury; GI, gastrointestinal; HE, hepatic encephalopathy; HRS-AKI, hepatorenal syndrome-acute kidney injury; INR, international normalized ratio; KCC, King's College Criteria; MELD, Model for End-Stage Liver Disease.

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Shingina et al., AJG, 2023  
Bajaj et al., AJG, 2022

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## 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

**Table 1. - Patient characteristics**

|   |             |
|---|-------------|
| Mean age (years)  | 50 ± 19     |
| Mean maximal ALT level (U/l)                              | 1797 ± 2214 |
| Mean maximal AST level (U/l)                              | 2288 ± 5571 |
| Mean maximal GGT level (U/l)                              | 665 ± 846   |
| Mean maximal ALP level (U/l)                              | 304 ± 278   |
| Mean minimal albumin level (g/dl)                         | 2.6 ± 0.7   |
| Mean INR  | 2.17 ± 0.78 |
| Mean maximal bilirubin level (mg/dl)                      | 18.4 ± 12.3 |
| Mean platelet count (/nl)                                 | 174 ± 85    |
| Mean IgG level (mg/dl)                                    | 1324 ± 691  |
| Patients with acute liver failure (ALF)                   | 6 (9%)      |
| Patients with acute liver injury (ALI)                    | 60 (91%)    |
| Patients died   | 9 (14%)     |
| Patients undergone liver transplantation                  | 0 (0%)      |
| Biopsy via transjugular route                             | 13 (20%)    |
| Bleeding complication after biopsy via transjugular route | 1 (7.7%)    |
| Biopsy via percutaneous route                             | 53 (80%)    |
| Bleeding complication after biopsy via percutaneous route | 1 (1.9%)    |

Hunyady et al., Eur Gastro and Hep, 2022

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## 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

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## ALF Work up

- History, history, history
  - Exposures
  - Medication reviews
  - Collateral
- Consult to GI/Hepatology

**Table 8. Initial diagnostic workup**

|                      | Laboratory analysis  | Imaging   | Consultations  |
|----------------------|--|---|--|
| All patients         | General <ul style="list-style-type: none"> <li>• CBC, CMP, Mg, PO4, LDH, CK</li> <li>• INR, Fibrinogen, PT</li> <li>• ABG, arterial lactate</li> <li>• Blood culture, urine culture</li> <li>• ABO match and screen</li> <li>• Serum beta-hCG (all females)</li> </ul> Viral <ul style="list-style-type: none"> <li>• HAV IgM, HBsAG, HBeIgM, HBV PCR, HCV PCR, HEV PCR (if endemic)</li> <li>• EBV PCR, CMV PCR, HSV PCR, VZV PCR</li> </ul> Toxicology <ul style="list-style-type: none"> <li>• Serum acetaminophen</li> <li>• Serum ASA</li> <li>• Urine drug screening</li> </ul> Autoimmune <ul style="list-style-type: none"> <li>• ANA, F-Actin</li> <li>• IgG, IgM, IgA</li> </ul> Metabolic <ul style="list-style-type: none"> <li>• Ceruloplasmin</li> <li>• Ferritin</li> </ul> | ECG<br>CXR<br>Abdominal ultrasound with Doppler<br>CT head (if encephalopathy)<br>Consider contrasted imaging                 | Hepatology<br>Gastroenterology<br>ICU<br>Contact transplant center |
| Transplant candidate | HIV, QuantiFERON gold, cryptococcal antigen, treponemal antibody, second ABO match, and screening  | Contrasted imaging if renal function allows<br>TTE<br>Repeat CT head with any change in mental status<br>Consider ICP monitor | Psychiatry<br>Social work<br>Hepatobiliary surgery                 |

ANA, antinuclear antibody; CBC, complete blood count; CK, creatinine kinase; CMP, comprehensive metabolic panel; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HEV, viral hepatitis E; HSV, herpes simplex virus; ICP, intracranial pressure; ICU, Intensive Care Unit; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; INR, international normalized ratio; LDH, lactate dehydrogenase; PCR, polymerase chain reaction; PT, prothrombin time; TTE, transthoracic echocardiogram; VZV, varicella zoster virus.

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Shingina et al., AIG, 2023

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# Management: CNS

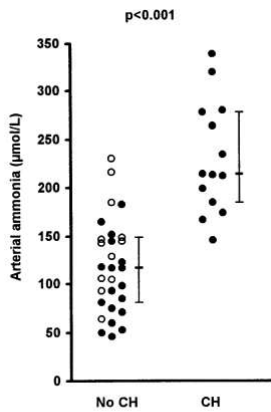


FIG. 1. Arterial plasma ammonia concentration in 30 patients who did not develop cerebral herniation (No CH) and 14 patients who died from cerebral herniation (CH). The error bars to the left of each group are median, 25th, and 75th percentiles. (○), Patients who underwent liver transplantation (n = 7); (●) patients who died from other reasons (n = 5).

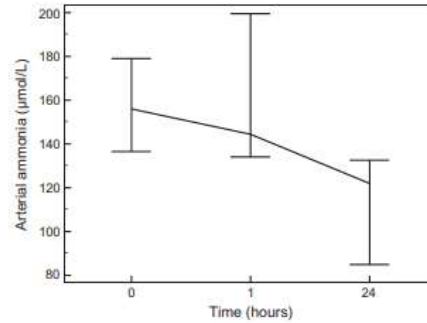


Fig. 3. Changes in arterial ammonia concentration after 1 and 24 h after the initiation of continuous veno-venous haemofiltration. Arterial ammonia reported as median (interquartile range) concentration.

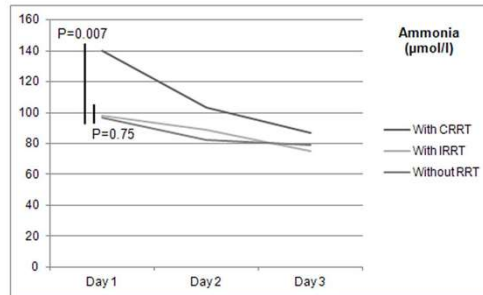
Slack et al., *Hepatology*, 1999  
Slack et al., *Liver International*, 2014  
Cardoso et al., *Hepatology*, 2018

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# Management: CNS

Baseline characteristics of patients with acute liver failure at study admission (n=1186).

|                          | n    | n (%) or median (IQR) |                      |                         | P*     |
|--------------------------|------|-----------------------|----------------------|-------------------------|--------|
|                          |      | Overall (n=1186)      | RRT on Day 1 (n=314) | No RRT on Day 1 (n=872) |        |
| Age                      | 1186 | 39 (29-52)            | 38 (28-50)           | 40 (29-52)              | 0.15   |
| Sex (female)             | 1186 | 819 (69%)             | 212 (68%)            | 607 (70%)               | 0.49   |
| Race                     | 1186 |                       |                      |                         | 0.12   |
| White                    |      | 878 (74%)             | 234 (75%)            | 644 (74%)               |        |
| African-american         |      | 184 (16%)             | 40 (13%)             | 144 (17%)               |        |
| Other                    |      | 124 (11%)             | 40 (13%)             | 84 (10%)                |        |
| Etiology (acetaminophen) | 1186 | 593 (50%)             | 169 (54%)            | 424 (49%)               | 0.11   |
| HE grades 3-4            | 1186 | 600 (51%)             | 223 (71%)            | 377 (43%)               | <0.001 |
| Organ support            |      |                       |                      |                         |        |
| Mechanical Ventilation   | 1186 | 632 (53%)             | 254 (81%)            | 378 (43%)               | <0.001 |
| Vasopressors             | 1186 | 299 (25%)             | 176 (56%)            | 123 (14%)               | <0.001 |
| Biochemistry (admission) |      |                       |                      |                         |        |
| Ammonia (µmol/l)         | 1186 | 97 (63-157)           | 110 (68-185)         | 95 (61-144)             | <0.001 |
| INR                      | 1186 | 2.8 (2.1-4.2)         | 2.9 (2.1-4.3)        | 2.7 (2.1-4.1)           | 0.38   |



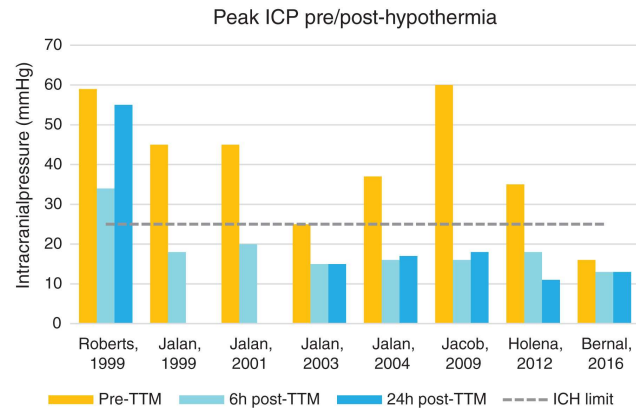
| Ammonia Cut off micromole/L | Sensitivity | Specificity |
|-----------------------------|-------------|-------------|
| 100                         | 77%         | 55%         |
| 150                         | 58%         | 76%         |
| 200                         | 42%         | 87%         |

CCardoso et al., *Hepatology*, 2018

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# 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).



Ribaud et al., Nurs in Crit Care, 2023

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# Management: CNS ICP Monitors

| Year of publication | Author           | Single or multi-center                            | Number of patients | Type of invasive monitor used   | Coagulopathy reversal strategy   | Consistent use of a single protocol? | Post-procedure imaging required in all patients? | Incidence of intracranial hemorrhage  | Incidence of elevated ICP |
|---------------------|------------------|---|--------------------|---|--|--------------------------------------|--|---|---------------------------|
| 2012                | Kamat et al.     | Single-center                                     | 14 children        | Intraparenchymal 100%   | rFVIIa plus FFP within 30 mins prior to procedure to achieve INR ≤1.5; vitamin K | Yes                                  | Not reported                                     | Symptomatic 7%  | Not reported              |
| 2014                | Karvellas et al. | Multi-center (ALFSG)                              | 140                | Subdural 27%; intraparenchymal 24%; epidural 23%; lumbar 17%; external ventricular drain 9% | FFP 84%; platelet transfusion 43%; rFVIIa 2%                                     | No                                   | No   | Symptomatic 7%  | 51%                       |
| 2016                | Maloney et al.   | Single-center                                     | 20                 | Intraparenchymal 65%; epidural 35%  | FFP and rFVIIa to goal INR ≤1.5; platelet transfusion to goal 50,000/μL          | Not reported                         | No   | Overall 15% reported. intraparenchymal - 2 of 10 (20%) with imaging available (both fatal); epidural 1 of 3 (33%) - with imaging available (asymptomatic) | 70%                       |
| 2016                | Bernal et al.    | Multi-center clinical trial of hypothermia in ALF | 43                 | Intraparenchymal 100%   | Not reported   | Not reported                         | No   | None - one remote hemorrhage in the temporal lobe   | 44%                       |
| Current study       | Rajajee et al.   | Single-center                                     | 24                 | Intraparenchymal 100%   | See Table 1  | Yes                                  | Yes  | 4% (symptomatic 0%)   | 54%                       |

Rajajee et al., Crit Care, 2018

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# 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

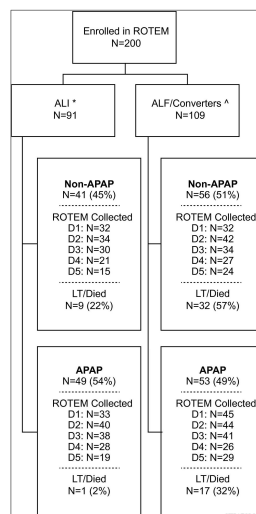
- In patients with ALF and grade 2 or higher encephalopathy, we suggest early CRRT for the management of hyperammonemia even in the absence of conventional RRT indications.  
**GRADE recommendation: conditional, very low quality of evidence.**

Shingina et al., AJG, 2023

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# 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



|                 | Admission     | Day 2         | Day 3         | Day 4         | Day 5         |
|-----------------|---------------|---------------|---------------|---------------|---------------|
| ALI             | 88 (75,112)   | 81 (69,101)   | 80 (66,94)    | 74 (60,90)    | 74 (62,88)    |
| ALF/Converters  | 193 (172,214) | 183 (160,211) | 181 (160,208) | 177 (160,204) | 190 (163,224) |
| Non-APAP        | 102 (74,156)  | 104 (81,178)  | 110 (72,158)  | 105 (76,152)  | 110 (77,179)  |
| APAP            | 102 (77,172)  | 112 (85,154)  | 104 (76,150)  | 101 (71,141)  | 111 (80,151)  |
| LT/Died         | 71 (54,76)    | 72 (63,75)    | 71 (62,76)    | 71 (65,75)    | 70 (63,76)    |
| Non-APAP        | 71 (63,79)    | 70 (63,79)    | 71 (66,77)    | 70 (67,79)    | 70 (62,76)    |
| APAP            | 95 (47,61)    | 54 (47,60)    | 54 (46,61)    | 54 (47,61)    | 53 (46,62)    |
| LT/Died         | 52 (47,60)    | 52 (46,58)    | 53 (46,58)    | 53 (46,58)    | 52 (46,58)    |
| Bleeding Absent | 153 (8,91)    | 116 (9,18)    | 116 (10,21)   | 116 (11,21)   | 112 (11,21)   |

|                | Admission     | Day 2         | Day 3         | Day 4         | Day 5         |
|----------------|---------------|---------------|---------------|---------------|---------------|
| ALI            | 85 (4,100)    | 80 (68,96)    | 74 (63,93)    | 73 (62,89)    | 71 (61,86)    |
| ALF/Converters | 308 (170,208) | 279 (158,204) | 281 (159,205) | 273 (158,198) | 276 (162,214) |
| Non-APAP       | 102 (71,171)  | 103 (80,183)  | 103 (71,159)  | 101 (74,158)  | 111 (74,188)  |
| APAP           | 97 (71,177)   | 106 (71,174)  | 103 (68,149)  | 101 (69,146)  | 110 (89,169)  |
| LT/Died        | 70 (64,76)    | 72 (63,75)    | 72 (62,77)    | 70 (65,76)    | 70 (64,76)    |
| Non-APAP       | 72 (61,78)    | 72 (63,79)    | 72 (63,77)    | 72 (66,78)    | 71 (69,78)    |
| APAP           | 57 (46,61)    | 54 (47,61)    | 53 (47,61)    | 55 (47,61)    | 54 (47,63)    |
| LT/Died        | 53 (46,68)    | 53 (46,58)    | 53 (46,59)    | 54 (46,60)    | 54 (46,61)    |
| TFS            | 111 (10,16)   | 110 (10,16)   | 112 (11,21)   | 111 (11,21)   | 112 (11,21)   |

Stravitz et al., Hepatology, 2021

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## 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.**

Shingina et al., AJG, 2023

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## 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

Comparison of 226 patients with bloodstream infections with 1325 patients without BSI

|                             | BSI (N=226)           | No BSI (N=1325)       | p-value |
|-----------------------------|-----------------------|-----------------------|---------|
| Age                         | 40.5 (30.0-51.0)      | 39.0 (29.0-50.0)      | 0.49    |
| Female                      | 143 (63.3%)           | 923 (69.7%)           | 0.06    |
| Etiology                    |                       |                       | 0.30    |
| APAP                        | 100 (44.3%)           | 619 (46.7%)           |         |
| Viral Hepatitis             | 15 (6.6%)             | 138 (10.4%)           |         |
| DILI                        | 27 (12.0%)            | 147 (11.1%)           |         |
| Indeterminate               | 34 (15.0%)            | 172 (13.0%)           |         |
| Other                       | 50 (22.1%)            | 249 (18.8%)           |         |
| Biochemistry*               |                       |                       |         |
| APACHE II                   | 17.0 (14.0-22.0)      | 15.0 (10.0-21.0)      | 0.02    |
| MELD                        | 31.7 (26.0-38.1)      | 31.7 (24.5-38.8)      | 0.96    |
| INR                         | 2.6 (1.9-4.1)         | 2.7 (2.0-4.2)         | 0.14    |
| Bilirubin (mg/dl)           | 7.6 (4.1-20.2)        | 7.3 (3.7-20.5)        | 0.50    |
| Creatinine (mg/dl)          | 1.8 (1.0-3.1)         | 1.6 (0.9-3.1)         | 0.14    |
| Lactate (mg/dl)             | 4.9 (2.8-10.9)        | 4.4 (2.5-9.5)         | 0.10    |
| ALT (U/L)                   | 1461.0 (492.5-3794.5) | 2076.5 (674.0-4645.0) | 0.02    |
| WBC                         | 10.3 (6.8-16.3)       | 10.5 (7.2-15.1)       | 0.86    |
| Platelet Count              | 120.0 (81.0-187.0)    | 133.0 (87.0-197.0)    | 0.07    |
|                             | BSI (N=226)           | No BSI (N=1325)       | p-value |
| Admission*                  | 50 (22.3%)            | 271 (20.7%)           | 0.57    |
| 7-days**                    | 79 (35.1%)            | 443 (33.6%)           | 0.65    |
| Antimicrobial Prophylaxis** | 77 (34.1%)            | 523 (39.5%)           | 0.12    |
| Coma Grade*                 |                       |                       | 0.002   |
| 1 or 2 (Low)                | 96 (42.5%)            | 711 (53.8%)           |         |
| 3 or 4 (High)               | 130 (57.5%)           | 610 (46.2%)           |         |

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

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# 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

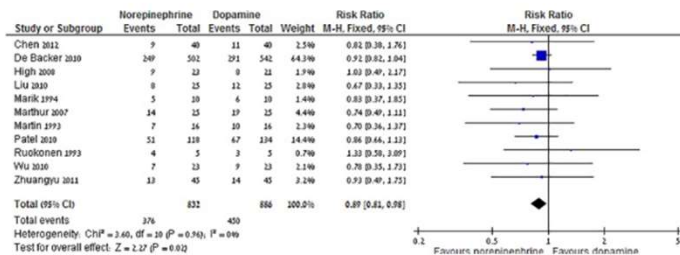
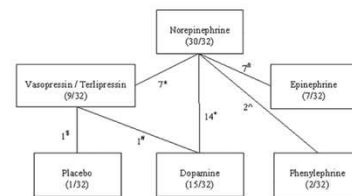
- In patients with ALF, we recommend against the routine use of prophylactic antimicrobial agents given no improvement in either rate of bloodstream infection or 21-day mortality. **GRADE recommendation: conditional, low quality of evidence.**

Shingina et al., AJG, 2023

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# Management: Hemodynamics and Renal Failure

- Similar to septic shock
  - high cardiac output
  - low systemic vascular resistance
  - decreased effective circulating volume



Norepinephrine vs. dopamine 28d mortality

# open-label dobutamine allowed  
 open-label vasopressors allowed  
 open-label vasopressors and dobutamine allowed  
 open-label dobutamine allowed in 6/7 trials, open-label vasopressors allowed 3/7 trials  
 open-label vasopressors allowed 6/7 trials  
 open-label vasopressors allowed 4/14 trials and not stated in 7/14 trials, forbidden in 3/14 trials

Abni et al., Plos One, 2015

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# 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**

Shingina et al., AJG, 2023

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# Management: DILI

## • Idiosyncratic DILI

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

TABLE 3 - The Implicated HDSs in Waitlisted Patients With DIALF During 1995-2020

| HDS                              | Overall | 1995-2003 | 2004-2012 | 2013-2020 |
|----------------------------------|---------|-----------|-----------|-----------|
|                                  | n = 61  | n = 7     | n = 19    | n = 35    |
| Herbal agent unspecified         | 27      | 3         | 10        | 14        |
| Weight loss                      | 7       | 1         | 2         | 4         |
| Herbal tea                       | 5       | 1         | 2         | 2         |
| Oxylite Pro                      | 4       | None      | None      | 4         |
| Hydroxycut                       | 3       | None      | 2         | 1         |
| Green tea extract                | 2       | None      | None      | 2         |
| Muscle building                  | 2       | None      | None      | 2         |
| Banaba                           | 1       | None      | 1         | None      |
| Cleansing                        | 1       | None      | None      | 1         |
| Energy enhancer                  | 1       | None      | None      | 1         |
| Garcinia cambogia                | 1       | None      | None      | 1         |
| Kamdudha Ras/Mahamanjstadi Kwath | 1       | None      | 1         | None      |
| Kava                             | 1       | 1         | None      | None      |
| Khat                             | 1       | None      | None      | 1         |
| Lipolyze                         | 1       | None      | 1         | None      |
| Maca root                        | 1       | 1         | None      | None      |
| Nerve renew                      | 1       | None      | None      | 1         |
| Tesla                            | 1       | None      | None      | 1         |

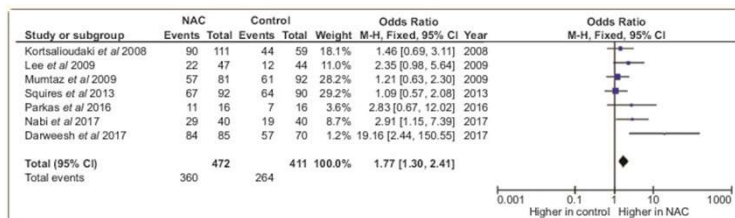
Abni et al., Plos One, 2015  
Walayaet et al., Ann of Gastro, 2021

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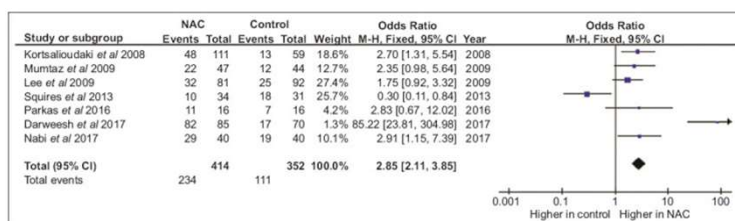


## Management: DILI

| Etiology  | N-acetylcysteine | Control | Total |
|---|------------------|---------|-------|
| Drug-induced liver failure                              | 48               | 45      | 102   |
| Viral hepatitis   | 115              | 98      | 213   |
| Autoimmune  | 15               | 17      | 32    |
| Metabolic   | 29               | 16      | 45    |
| Other (infection, undetermined, pregnancy-related etc.) | 139              | 145     | 284   |



Overall Survival



Transplant Free Survival

Walayat et al., Ann of Gastro, 2021

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## 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.  
**GRADE recommendation: strong, moderate quality of evidence**

Shingina et al., AJG, 2023

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## 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

|                 |   |
|-----------------|---|
| Acute AIH       | Icteric<br>No coagulopathy<br>No encephalopathy           |
| AS-AIH          | Icteric<br>Coagulopathic (INR ≥ 1.5)<br>No encephalopathy |
| AS-AIH with ALF | Icteric<br>Coagulopathic (INR ≥ 1.5)<br>Encephalopathic   |

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

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## Management AIH

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

Rahim et al., LTx, 2019

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# 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.

Shingina et al., AJG, 2023

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# 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 11. Prognostic models

| Prognostic model  | Individual constituents  | Comments regarding use  |
|---|--|---|
| MELD score  | INR, TB, creatinine  | MELD >33 for APAP-induced and MELD >32 for non-APAP-induced ALF<br>Sensitivity 74%<br>Specificity 67% |
| King's College Criteria<br>APAP-induced ALF<br>Non-APAP-induced ALF | Arterial pH (<7.3 after resuscitation), lactate (>3 mmol/L)<br>OR all of the following: HE (>grade 3), creatinine (>3.4 mg/dL), INR >6.5<br>INR (>6.5) OR three-fifths of the following etiology (indeterminant, DILI), age (>40), jaundice to encephalopathy time (>7 days), TB (>17.4 mg/dL), INR (>3.5)   | Sensitivity 65%<br>Specificity 93%<br>Sensitivity 68%<br>Specificity 82%                              |
| Clichy Criteria   | HE and factor V (<20%) in age <30 OR factor V (<30%) in age >30  | Sensitivity 56% for APAP-ALF<br>Sensitivity 50% for non-APA ALF                                       |
| Escudie Criteria (mushrooms)  | • Interval between ingestion and diarrhea <8 hr or<br>• A decrease in prothrombin index <10% of normal (approximately an INR >6 ≥ 4 d after ingestion)   | One should not wait on the development of encephalopathy to determine transplant evaluation.          |
| Swansea Criteria (ALFP)   | <ul style="list-style-type: none"> <li>• Vomiting</li> <li>• Abdominal pain</li> <li>• Polydipsia/polyuria</li> <li>• Encephalopathy</li> <li>• Elevated bilirubin &gt;14 μmol/L</li> <li>• Hypoglycemia &lt;4 mmol/L</li> <li>• Elevated urea &gt;340 μmol/L</li> <li>• Leukocytosis &gt;11 × 10<sup>9</sup></li> <li>• Ascites or bright liver on ultrasound</li> <li>• Elevated transaminase &gt;42 IU/L</li> <li>• Elevated ammonia &gt;47 μmol/L</li> <li>• Renal impairment: Creatinine &gt;150 μmol/L</li> <li>• Coagulopathy: PT &gt;14 seconds or APPT &gt;34s</li> <li>• Microvesicular steatosis on liver biopsy</li> </ul> | 6 or more findings are required in the absence of another cause                                       |

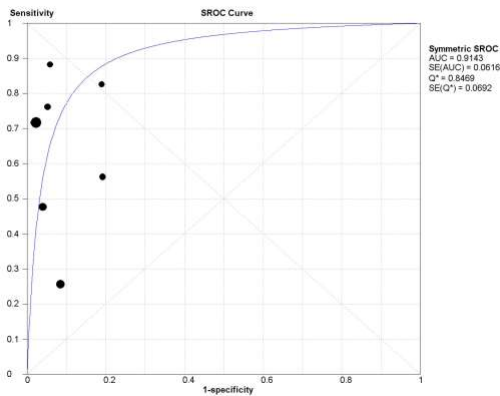
ALF, acute liver failure; ALFP, acute fatty liver of pregnancy; APAP, N-acetyl-p-aminophenol; DILI, drug-induced liver injury; HE, hepatic encephalopathy; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease.

Shingina et al., AJG, 2023

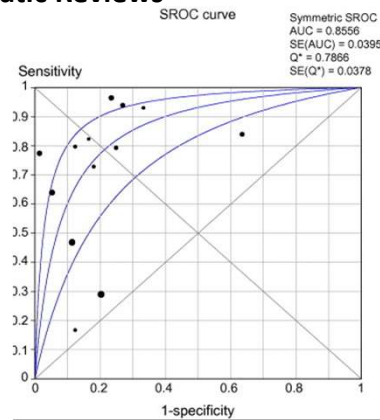
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# Liver Transplant Considerations: KCC

## King College Criteria Systematic Reviews



APAP ALF



Non-APAP ALF

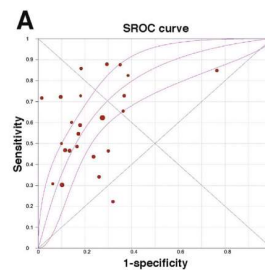
Craig et al., Alim Pharm and Ther, 2010  
McPhail et al., J Hep, 2010

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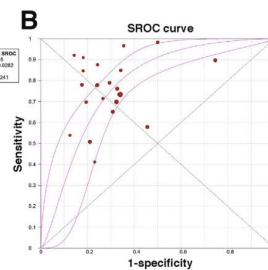
# Liver Transplant Considerations: MELD

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

| Study                   | KCC              |                  |                  | MELD             |                  |                  |
|-------------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                         | Sensitivity      | Specificity      | DOR              | Sensitivity      | Specificity      | DOR              |
| Plémez-Luna et al, 2006 | 0.46             | 0.70             | 2.02             | 0.71             | 0.73             | 6.88             |
| Taylor et al, 2006      | 0.31             | 0.94             | 6.67             | 0.54             | 0.86             | 8.17             |
| Zaman et al, 2006       | 0.73             | 1.00             | —                | 0.97             | 0.86             | 50.91            |
| Diemen et al, 2007      | 0.47             | 0.88             | 6.73             | 0.76             | 0.87             | 6.55             |
| Katoonzadeh et al, 2007 | 0.87             | 0.64             | 12.92            | 0.86             | 0.75             | 21.78            |
| Schmidt & Larsen, 2007  | 0.55             | 0.83             | 5.76             | 0.58             | 0.54             | 1.63             |
| Wei et al, 2007         | 0.30             | 0.90             | 3.80             | 0.70             | 0.68             | 4.83             |
| Yaricom et al, 2007     | 0.73             | 0.82             | 12.00            | 0.91             | 0.82             | 45.00            |
| Hadem et al, 2008       | 0.58             | 0.82             | 6.51             | 0.65             | 0.69             | 4.19             |
| Yamagishi et al, 2009   | 0.82             | 0.62             | 7.47             | 0.41             | 0.77             | 2.33             |
| Bechmann et al, 2010    | 0.22             | 0.68             | 0.61             | 0.77             | 0.76             | 11.08            |
| Kumar et al, 2010       | 0.34             | 0.74             | 1.46             | 0.73             | 0.67             | 5.50             |
| Chen et al, 2011        | 0.65             | 0.64             | 3.31             | 0.85             | 0.82             | 24.75            |
| Cholongitas et al, 2012 | 0.47             | 0.87             | 5.61             | 0.89             | 0.25             | 2.95             |
| Craig et al, 2012       | 0.86             | 0.82             | 26.57            | 1.00             | 0.50             | —                |
| Hadem et al, 2012       | 0.44             | 0.76             | 2.50             | 0.51             | 0.79             | 3.86             |
| Kumar et al, 2012       | 0.62             | 0.73             | 4.34             | 0.73             | 0.66             | 5.34             |
| Parkash et al, 2012     | 0.88             | 0.71             | 17.14            | 0.79             | 0.71             | 9.00             |
| Shahk et al, 2012       | 0.85             | 0.24             | 1.71             | 0.78             | 0.82             | 16.51            |
| Manshadi et al, 2013    | 0.72             | 0.90             | 24.27            | 0.78             | 0.76             | 10.97            |
| Feng et al, 2014        | 0.49             | 0.83             | 4.71             | 0.70             | 0.81             | 9.53             |
| Manjrekar et al, 2014   | 0.74             | 0.63             | 4.42             | 0.86             | 0.66             | 10.72            |
| Baghi et al, 2015       | 0.60             | 0.86             | 9.00             | 0.92             | 0.86             | 69.00            |
| Pooled results (95% CI) | 0.59 (0.56-0.62) | 0.79 (0.77-0.81) | 5.27 (3.67-7.57) | 0.74 (0.71-0.77) | 0.67 (0.64-0.69) | 7.01 (5.06-9.71) |



KCC  
AUC 0.76



MELD  
AUC 0.78

McPhail et al., Clin Gastro Hep, 2016

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## 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.

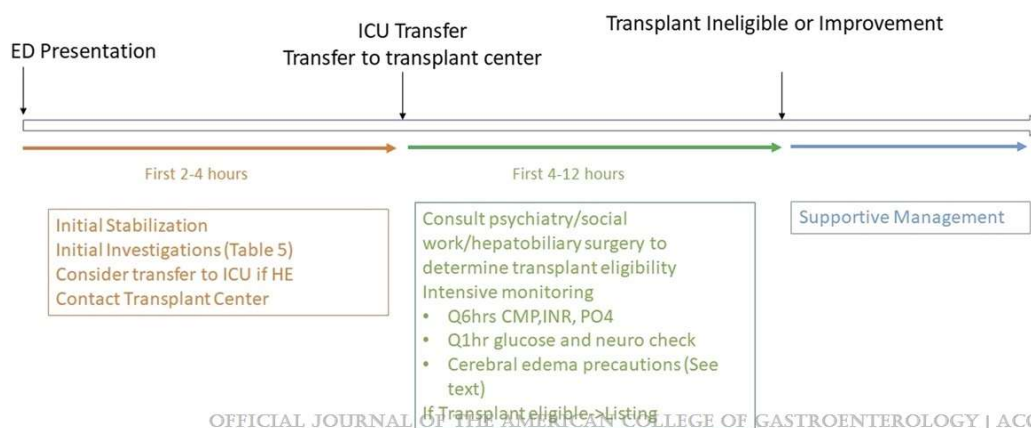
### Recommendations

- 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

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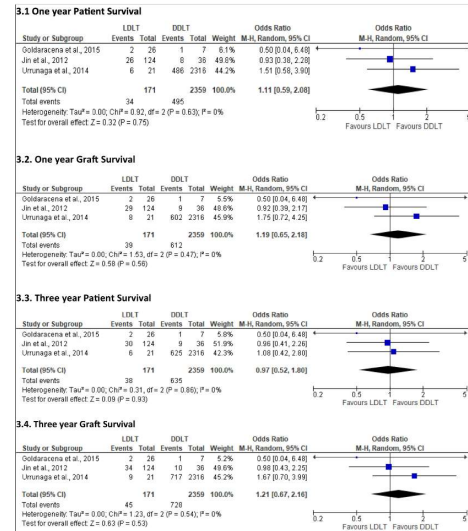
## Evaluation Timeline



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## 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



Shingina et al., Trans Rev, 2022

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## 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.

Shingina et al., AJG, 2023


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## Questions



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