ALF Etiology	First-Tier/Screening Test(s)*	Second-Tier/Confirmatory Test(s)
Paracetamol	Serum paracetamol concentration[1]	Paracetamol-hepatocyte protein adducts[2]
Ischemia	Blood pressure history, echocardiogram	Enzyme pattern, rapid recovery
HAV	IgM anti-HAV	
HBV	IgM anti-HBc, HBsAg, anti-HDV	HBV DNA, HDV RNA
HEV	IgM anti-HEV	HEV RNA
DILI	History of known hepatotoxin ingestion, exclude other causes	Liver biopsy
AI-ALF	ANA, ASMA, immunoglobulins	Liver biopsy
Wilson Disease	Slit-lamp exam of the eyes, hemoglobin ≤10g/dl, Alk P/Bili ratio < 4	24 hr urinary copper; liver biopsy, quantitative liver copper
Budd-Chiari Syndrome	Doppler US of hepatic circulation	Hepatic venogram
Pregnancy (AFLP/HELLP)	Third trimester of pregnancy, pre-eclampsia, coagulopathy	Ultrasound
HSV	IgM anti-HSV 1/2	Blood HSV DNA PCR
Malignancy	CT or MRI (hepatomegaly)	Liver biopsy

Appendix Table 1. **Screening and confirmatory testing for patients presenting with ALF.**

*The critical importance of a detailed history and physical exam and standard biochemistries is implied for all etiologies.

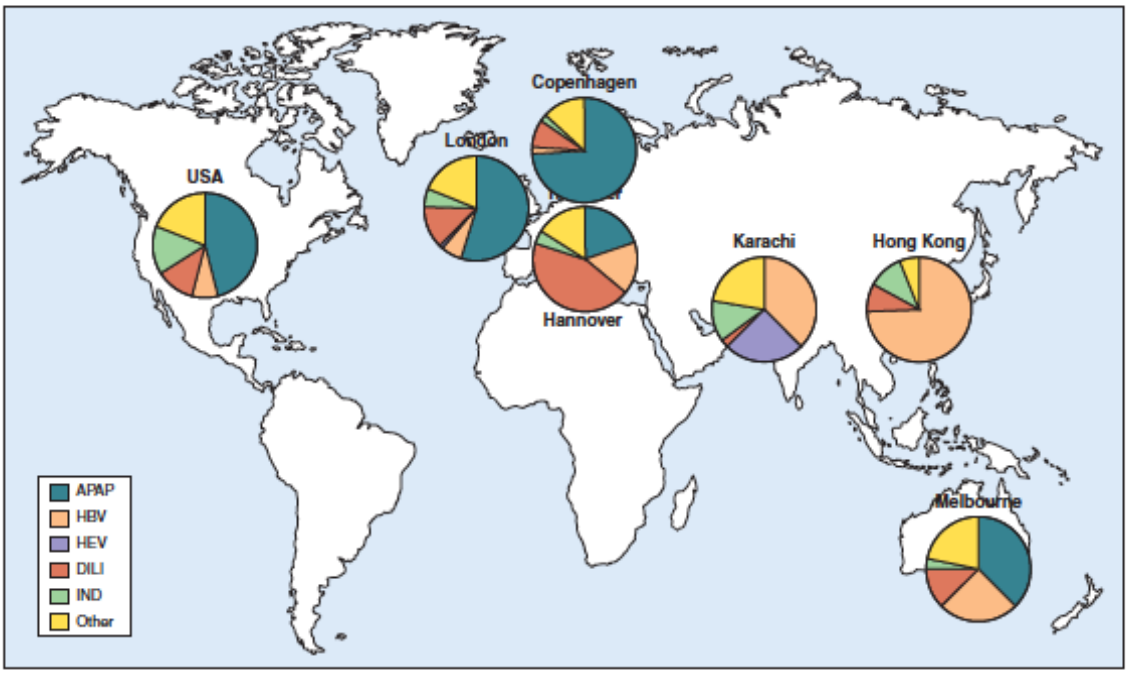
AFLP, acute fatty liver of pregnancy; ANA, antinuclear antibodies; ASMA, anti-smooth muscle antibodies; hGC, human chorionic gonadotropin; HELLP, hemolysis-elevated liver enzyme-low platelet syndrome; HEV, hepatitis E virus.

Etiology	Potential Treatment	Comments/References
Pregnancy-Associated ALF	Delivery	Generally effective but may progress to ALF after delivery[3,4,5]
Hepatitis B Virus	Lamivudine, other nucleos(t)ide analogues	Negative randomized, controlled study[6]
Herpes Simplex Virus	Acyclovir	Anecdotal response, overall very poor prognosis[7]
Amanita phalloides (mushrooms)	Silibinin, penicillin	Anecdotal responses[8,9]
Autoimmune-ALF	Corticosteroids	Anecdotal response, but series suggest limited benefit.[10] May increase peri-transplant sepsis.[11]

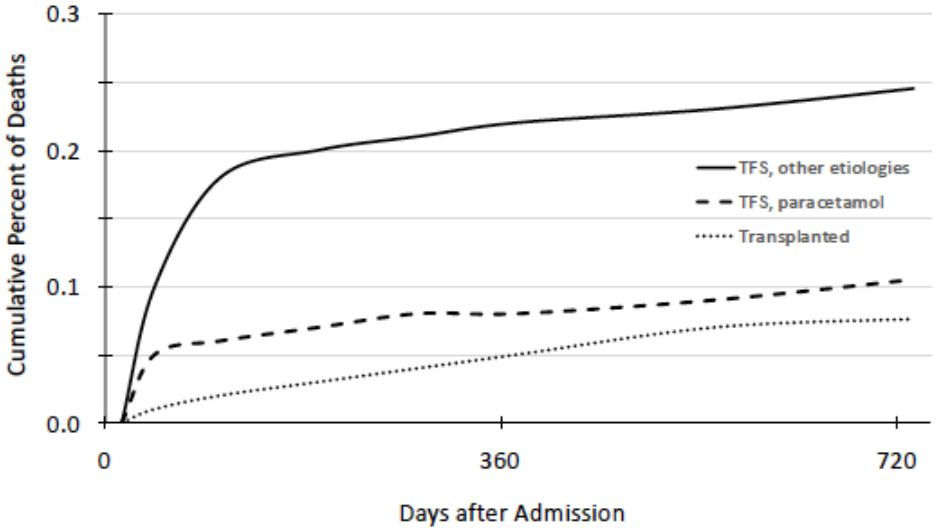
Appendix Table 2. **Etiology-specific treatments of non-paracetamol-induced ALF**. *N*-acetylcysteine may be used in adults for non-paracetamol ALF, based on at least one randomized trial.[12]

Prophylaxis	Elevate head-of-bed 30^{o} Maintain neck in neutral rotation Allow spontaneous hyperventilation (PCO_2 ~25mmHg)[13] Allow spontaneous hypothermia (34-36ºC) Induce mild hypernatremia to [Na] 145-155 mEq/L[14]
Treatment: **First-line therapy**	Mannitol (0.5-1.0 gm/kg body weight IV)[15] Hypertonic saline boluses[16] Continuous renal replacement therapy[17]
Treatment: **Rescue therapy**	Additional mannitol boluses Deeper sedation/Barbiturate coma[18] Therapeutic hypothermia (32-34°C)[19] Indomethacin (25 mg bolus IV)[20]

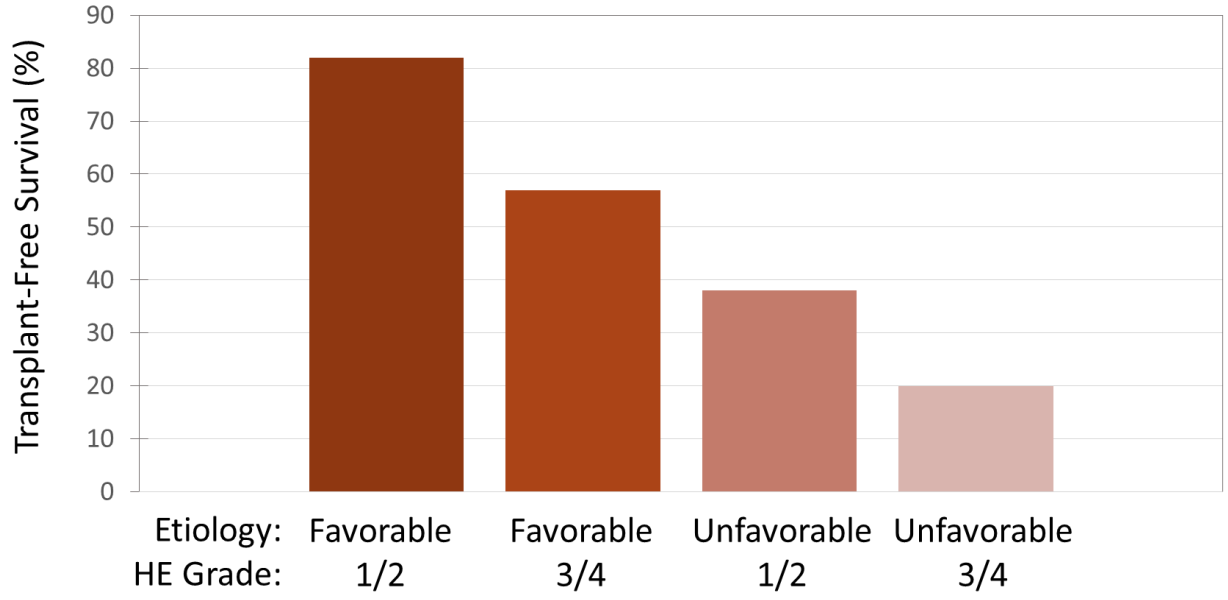
Appendix Table 3. **Prophylaxis against, and treatment of, cerebral edema in patients with ALF.** The use of intravenous indomethacin, which is not available in the US, is not discussed in the text.[20]



Appendix Figure 1. **Differences in etiology of acute liver failure worldwide.** While DILI and paracetamol dominate in the West, hepatitis B and E are prevalent in South Asia, hepatitis B in Asia and a blend of East and West in Australia (Reprinted with permission from Appendix reference 21).



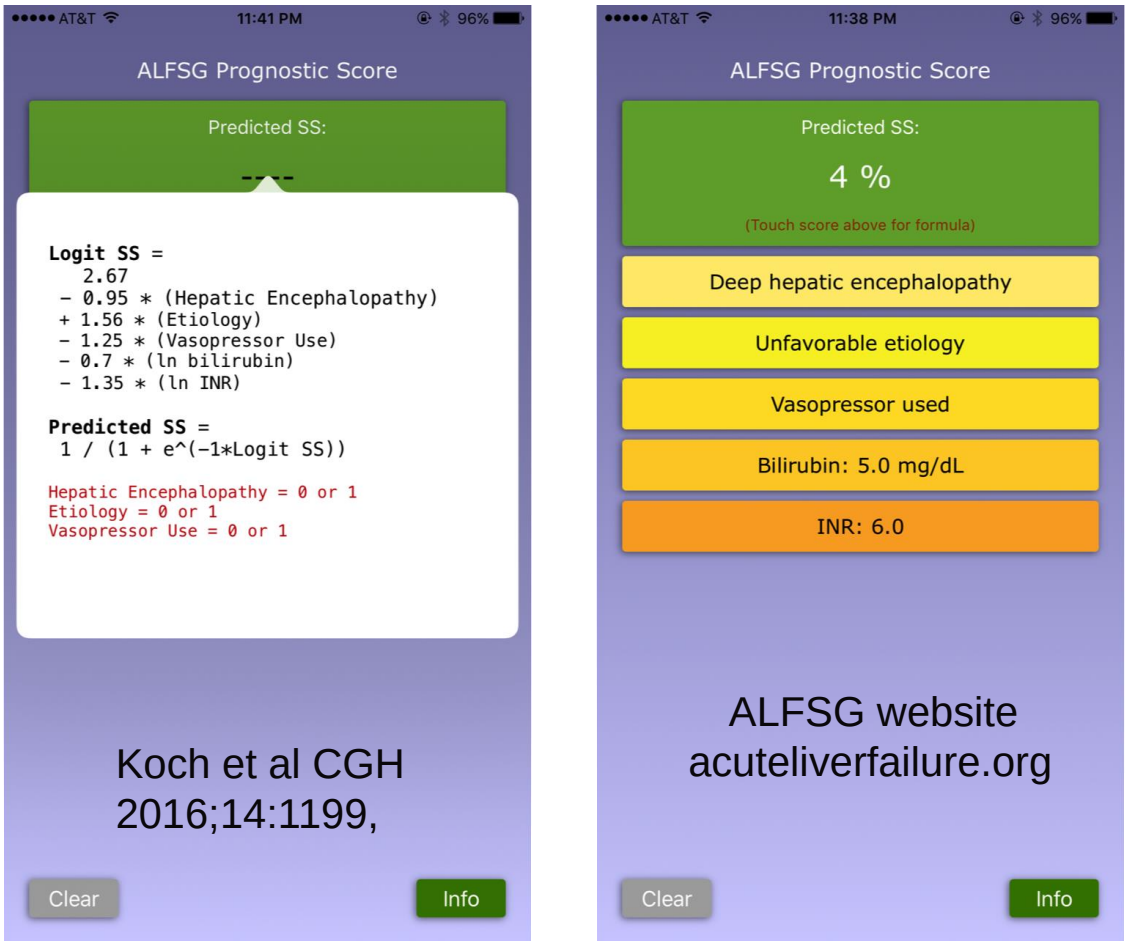
Appendix Figure 2**. Mortality in long-term follow-up of patients in the ALF Study Group Registry.** Actuarial 2-year mortality among 773 patients with acute liver failure who survived 21 days after admission to the ALF Study Group Registry. Liver transplant recipients (dotted line) had the lowest 2-year mortality (7.6%) compared to non-transplanted survivors of paracetamol overdose (dashed line; 10.5%) or non-transplanted survivors of non-paracetamol acute liver failure (solid line; 25.0%, P <0.0001) (adapted from Appendix reference 22, with permission). (TFS, transplant-free survivors at 21 days of admission).



Appendix Figure 3**. Transplant-free survival at 21 days after enrollment into the ALF Study Group Registry: Relationship of outcome to etiology of liver injury and grade of hepatic encephalopathy on admission.** Data from the ALF Study Group Registry.[23]

Favorable etiologies are those with higher spontaneous (transplant-free) survival, generally well above 50% and include paracetamol overdose, ischemia, hepatitis A, and pregnancy-associated acute liver failure. Unfavorable etiologies include acute liver failure due to all other causes and carry transplant-free survival rates < 25% (Table 1). HE, hepatic encephalopathy.

Appendix Figure 4. **Screen shot of the application for determining ALF Prognosis using the ALFSG Prognostic Index, predicting the likelihood of survival without transplantation, appendix reference 23.** The first three determinants are binary (yes/no) with the favorable and unfavorable etiologies listed on the pull-down menu. The last two are numerical values.



Appendix Figure 5. **Screenshot of the application for determining ALF Prognosis using the ALFSG Prognostic Index,[23] predicting the likelihood of survival without transplantation.** The calculations used and the reference is shown on the left and an example of use of the app is on the right.

Appendix References

1. Leventhal TM, Gottfried M, Olson JC, Subramanian RM, Hameed B, Lee WM. Acetaminophen is undetectable in plasma from more than half of patients believed to have acute liver failure due to overdose. *Clin Gastroenterol Hepatol* 2019 Feb 4. Epub ahead of print.
2. Khandelwal N, James LP, Sanders C, Larson AM, Lee WM. Unrecognized acetaminophen toxicity as a cause of indeterminate acute liver failure. *Hepatology* 2011;**53**:567-576.
3. Westbrook RH, Yeoman AD, Joshi D, et al. Outcomes of severe pregnancy-related liver disease: refining the role of transplantation. *Am J Transplant* 2010;**10**:2520-2526.
4. Zarrinpar A, Farmer DG, Ghobrial RM, et al. Liver transplantation for HELLP syndrome. *Am Surg* 2007;**73**:1013-1016.
5. Nelson DB, Yost NP, Cunningham FG. Acute fatty liver of pregnancy: clinical outcomes and expected duration of recovery. *Am J Obstet Gynecol* 2013;**209**:456-457.
6. Kumar M, Satapathy S, Monga R, et al. A randomized controlled trial of lamivudine to treat acute hepatitis B. *Hepatology* 2007;**45**:97-101.
7. Ichai P, Afonso AM, Sebagh M, Gonzalez ME, Codes L, Azoulay D, et al. Herpes simplex virus-associated acute liver failure: a difficult diagnosis with a poor prognosis. *Liver Transpl* 2005;**11**:1550-1555.
8. Montanini S, Sinardi D, Pratico C, Sinardi AU, Trimarchi G. Use of acetylcysteine as the life-saving antidote in Amanita phalloides (death cap) poisoning. Case report on 11 patients. *Arzneimittelforschung* 1999;**49**:1044-1047.
9. Broussard CN, Aggarwal A, Lacey SR, et al. Mushroom poisoning--from diarrhea to liver transplantation. *Am J Gastroenterol* 2001;**96**:3195-3198.
10. Karkhanis J, Verna EC, Chang MS, et al. Steroid use in acute liver failure. *Hepatology* 2014;**59**:612-621.
11. Ichai P, Duclos-Vallee JC, Guettier C, et al. Usefulness of corticosteroids for the treatment of severe and fulminant forms of autoimmune hepatitis. *Liver Transpl* 2007;**13**:996-1003.
12. Lee WM, Hynan LS, Rossaro L, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology* 2009; **137:** 856–64.
13. Jalan R, Olde Damink SW, Deutz NE, Hayes PC, Lee A. Restoration of cerebral blood flow autoregulation and reactivity to carbon dioxide in acute liver failure by moderate hypothermia. *Hepatology* 2001;**34**:50-54.
14. Murphy N, Auzinger G, Bernel W, Wendon J. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. *Hepatology* 2004;**39**:464-470.
15. Lidofsky SD, Bass NM, Prager MC, Washington DE, Read AE, Wright TL, et al. Intracranial pressure monitoring and liver transplantation for fulminant hepatic failure. *Hepatology* 1992;**16**:1-7.
16. Wendon J, Lee W. Encephalopathy and cerebral edema in the setting of acute liver failure: pathogenesis and management. *Neurocrit Care* 2008;**9**:97-102.
17. Cardoso FS, Gottfried M, Tujios S, Olson JC, Karvellas CJ. Continuous renal replacement therapy is associated with reduced serum ammonia levels and mortality in acute liver failure. *Hepatology* 2018;**67**:711-720.

18. Forbes A, Alexander GJ, O'Grady JG, Keays R, Gullan R, Dawling S, et al. Thiopental infusion in the treatment of intracranial hypertension complicating fulminant hepatic failure. *Hepatology* 1989;**10**:306-310.
19. Jalan R, Olde Damink SW, Deutz NE, Hayes PC, Lee A. Moderate hypothermia in patients with acute liver failure and uncontrolled intracranial hypertension. *Gastroenterology* 2004;**127**:1338-1346.
20. Clemmesen JO, Hansen BA, Larsen FS. Indomethacin normalizes intracranial pressure in acute liver failure: a twenty-three-year-old woman treated with indomethacin. *Hepatology* 1997;**26**:1423-1425.
21. Tujios SR, Lee WM. Acute Liver Failure. In: Dooley JS, Lok ASF, Garcia-Tsao G, Pinzani M. Sherlock's Diseases of the Liver and Biliary System, 13th Edition. Hoboken NJ: *Wiley-Blackwell,* 2018, pp. 62-81.
22. Fontana RJ, Ellerbe C, Durkalski VE, et al. Two-year outcomes in initial survivors with acute liver failure: results from a prospective, multicentre study. *Liver Int* 2015;**35**:370-380.
23. Koch DG, Tillman H, Durkalski V, Lee WM, Reuben A. Development of a model to predict transplant-free survival of patients with acute liver failure. *Clin Gastroenterol Hepatol* 2016;**14**:1199-1206.