AASLD Position Paper: The Management of Acute Liver Failure

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Preamble

- - . : (1) - - , (2) A C A D - ,[1] (3) , - AA D D A A ,[2] (4) - . , - , . , , . . - , C AA D (1[3]). AA D.

Introduction

A (A F) - 2,000 . . . .[4] - , , - ; (≈20%) .[5] A . , 15% . C , - 65%.[5] B , A F . A , .

Definition

A F - , ≥1.5, (-) - <26 .[6] , - B , - - <26 . A . A 26 . (<7), (7-21) (>21 <26) - - . F , .[5]

Abbreviations: ALF, acute liver failure; NAC, N-acetylcysteine; HELLP, Hemolysis, Elevated Liver Enzymes, Low Platelets syndrome; ICH, intracranial hypertension; ICP, intracranial pressure; CT, computerized tomography; US ALFSG, United States Acute Liver Failure Study Group; CPP, cerebral perfusion pressure; MAP, mean arterial pressure; SIRS, systemic inflammatory response syndrome; FFP, fresh frozen plasma; rFVIIa, recombinant activated factor; GI, gastrointestinal; H2, histamine-2; PPI, proton pump inhibitors; CVVHD, continuous venovenous hemodialysis; APACHE, Acute Physiology and Chronic Health Evaluation; AFP, alpha fetoprotein; MELD, Model for End-stage Liver Disease.

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Received March 9, 2005; accepted March 10, 2005.

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Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.20703

Potential conflict of interest: Nothing to report.

Table 1. Quality of Evidence on Which a Recommendation Is Based[3]

Grade	Definition
I	Randomized controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case-control analytic studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinions of respected authorities, descriptive epidemiology

Diagnosis and Initial Evaluation

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Table 2. Initial Laboratory Analysis

Prothrombin time/INR
Chemistries
sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate glucose
AST, ALT, alkaline phosphatase, GGT, total bilirubin, albumin
creatinine, blood urea nitrogen
Arterial blood gas
Arterial lactate
Complete blood count
Blood type and screen
Acetaminophen level
Toxicology screen
Viral hepatitis serologies
anti-HAV IgM, HBSAg, anti-HBc IgM, anti-HEV§, anti-HCV*
Ceruloplasmin Level#
Pregnancy test (females)
Ammonia (arterial if possible)
Autoimmune markers
ANA, ASMA, Immunoglobulin levels
HIV status‡
Amylase and lipase

*Done to recognize potential underlying infection.

#Done only if Wilson disease is a consideration (*e.g.,* in patients less than 40 years without another obvious explanation for ALF); in this case uric acid level and bilirubin to alkaline phosphatase ratio may be helpful as well.

‡Implications for potential liver transplantation.

§If clinically indicated.

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.[15-18]
. , [19] -
, -
, .[20]
Recommendations , AC -
A F -
1. Patients with ALF should be admitted and monitored frequently, preferably in an ICU (III). . AC
2. Contact with a transplant center and plans to transfer appropriate patients with ALF should be initiated early in the evaluation process (III). , 48
3. The precise etiology of ALF should be sought to guide further management decisions (III). .[21] AC (140
/ 5% -
, 70 // 4 × 17)
(, ,
Determining Etiologies and Specific Therapies). A F
(,
E A F -
,[5]), AC (-
. 150 / 5% 15 ;
50 / 4
100 / 16).
A -
, [22] -
. -
Acetaminophen Hepatotoxicity *Recommendations*
A ***4. For patients with known or suspected acetaminophen overdose within 4 hours of presentation, give activated charcoal just prior to starting NAC (I).***
- ***5. Begin NAC promptly in all patients where the quantity of acetaminophen ingested, serum drug level or rising aminotransferases indicate impending or evolving liver injury (II-1).***
. A - ***6. NAC may be used in cases of acute liver failure in which acetaminophen ingestion is possible or when knowledge of circumstances surrounding admission is inadequate (III).***
; A F 10
/ . ,
3-4 / .[10] *Mushroom Poisoning*
; (*Amanita phalloides*)
3,500 / A F, -
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E) -
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A F. -
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- .[13] - (AC), . F . ,

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.[27,28] /

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70%-80% ,

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30-40 / / ( )
3 4 .[26] -

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[30]; ,

.[31]

Table 3. Some Drugs Which May Cause Idiosyncratic Liver Injury Leading to ALF

Isoniazid	Isoflurane
Sufonamides	Lisinopril
Phenytoin	Nicotinic acid
Statins	Imipramine
Propylthiouracil	Gemtuzumab
Halothane	Amphetamines/Ecstasy
Disulfiram	Labetalol
Valproic acid	Etoposide
Amiodarone	Flutamide
Dapsone	Tolcapone
Herbals*	Quetiapine
Didanosine	Nefazodone
Efavirenz	Allopurinol
Metformin	Methyldopa
Ofloxacin	Ketoconazole
PZA	
Troglitazone	
Diclofenac	

Combination agents with enhanced toxicity:
- Trimethoprim-sulfamethoxazole
- Rifampin-isoniazid
- Amoxicillin-clavulanate

*Some Herbal products/dietary supplements that have been associated with hepatotoxicity include:

Kava kava	Chaparral
Skullcap	Germander
Pennyroyal	Jin Bu Huan
Heliotrope	Rattleweed
Comfrey	Sunnhemp
Senecio	Impila
Greater celandine	Gum Thistle
He Shon Wu	Ma Huang
LipoKinetix	Bai-Fang herbs

Recommendation

7. In ALF patients with known or suspected mushroom poisoning, consider administration of penicillin G and silymarin (III).

8. Patients with acute liver failure secondary to mushroom poisoning should be listed for transplantation, as this procedure is often the only lifesaving option (III).

Drug Induced Hepatotoxicity

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- (3).

Recommendations

9. Obtain details (including onset of ingestion, amount and timing of last dose) concerning all prescription and non-prescription drugs, herbs and dietary supplements taken over the past year (III).

10. Determine ingredients of non-prescription medications whenever possible (III).

11. In the setting of acute liver failure due to possible drug hepatotoxicity, discontinue all but essential medications (III).

Viral Hepatitis

- (2) -
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: 12%; B 8%, A 4%).[5] A
D B
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B A
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(AA D
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B, [36]). -
A F.
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50% .
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.[37,38] [39] -
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Recommendations

12. Viral hepatitis A- and B- (and E-) related acute liver failure must be treated with supportive care as no virus-specific treatment has been proven effective (III).

13. Nucleoside analogs should be given prior to and continued for 6 months after completion of chemotherapy in patients with Hepatitis B surface antigen positivity to prevent reactivation/acute flare of disease (III).

14. Patients with known or suspected herpes virus or varicella zoster as the cause of acute liver failure should be treated with acyclovir (III).

Wilson disease

A F (2%-3%
A F). E
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>20 / . D -
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. -F
50%
A F .[40] -
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. A
(/) (/) (>2.0)
.[40,41] -
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A F ;
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.[40] A
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.[40,42]
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A F -
AA D -
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D
.[40]

Recommendations

15. Diagnostic tests for Wilson disease should include ceruloplasmin, serum and urinary copper levels, total bilirubin/alkaline phosphatase ratio, slit lamp examination for Kayser-Fleischer rings, and hepatic copper levels when liver biopsy is feasible (III).

16. Patients in whom Wilson disease is the likely cause of acute liver failure must be immediately placed on the liver transplant list (III).

Autoimmune hepatitis

, - A F. - , -

AA D D - A (A F).[43] A , - .[44,45] A . , . - (40-60 /),[43] .

Recommendations

17. When autoimmune hepatitis is suspected as the cause of acute liver failure, liver biopsy should be considered to establish this diagnosis (III).

18. Patients with acute liver failure due to autoimmune hepatitis should be treated with corticosteroids (prednisone, 40-60 mg/day) (I).

19. Patients should be placed on the list for transplantation even while corticosteroids are being administered (III).

Acute Fatty Liver of Pregnancy/HELLP (Hemolysis, Elevated Liver Enzymes, Low Platelets) Syndrome

A [46-49] - . A - , . , , . F - - . . - . / - . E - . , - . - , .[50] ( ) A F , ( ).[37] A F - .

Recommendation

20. For acute fatty liver of pregnancy or the HELLP syndrome, consultation with obstetrical services and expeditious delivery are recommended (III).

Acute Ischemic Injury

A , / , .[51] D . D - - - ,[52] ,[53] .[54] , - .[55] A . - . - , - .

Recommendation

21. In ALF patients with evidence of ischemic injury cardiovascular support is the treatment of choice (III).

Budd-Chiari Syndrome

B -C ( ) A F. A , . - (, , ,). , .[56] A - B -C , .

Recommendation

22. Hepatic vein thrombosis with hepatic failure is an indication for liver transplantation, provided underlying malignancy is excluded (II-3).

Malignant Infiltration

A F. . D , - . - .[57,58] A ,[59,60] ,[61] 58 .[62]

Recommendations

23. In patients with acute liver failure who have a previous cancer history or massive hepatomegaly, consider underlying malignancy and obtain imaging and liver biopsy to confirm or exclude the diagnosis (III).

Indeterminate Etiology

A F , , - , . -

Recommendation

24. If the etiological diagnosis remains elusive after extensive initial evaluation, liver biopsy may be appropriate to attempt to identify a specific etiology that might influence treatment strategy (III).

Therapy: General Considerations

Background

A F , , . D , , A F . .[63-65] B A F , - . - ,[66,67] A F.[68] AC A F,[69] .[70] AC - .[71] AC A F . A , - , , -

AC - - A F . B A F , - . - , C - . C , . . C , , ( ) . - - , .

Specific Issues. 4.

Central Nervous System

C (C) - A F.[72] - . C , - .[73] -

C A F . , - . / , - .[74] -

C A F. ; .

Prevention/Management of Elevated Intracranial Pressure (ICP).

C A F (- 5). C - . 25% 35% , 65% 75% .[75] A .[76]

Grades I-II. D -

Table 4. Intensive Care of Acute Liver Failure

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
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 for platelet counts $<10{,}000/mm^3$ or invasive procedures
Recombinant activated factor VII: possibly effective for invasive procedures
Prophylaxis for stress ulceration: give H2 blocker or PPI
Hemodynamics/Renal Failure
Pulmonary artery catheterization
Volume replacement
Pressor support (dopamine, epinephrine, norepinephrine) as needed to maintain adequate mean arterial pressure
Avoid nephrotoxic agents
Continuous modes of hemodialysis if needed
NAC, prostacyclin: effectiveness unknown
Vasopressin: not helpful in ALF; potentially harmful.
Metabolic Concerns
Follow closely: glucose, potassium, magnesium, phosphate
Consider nutrition: enteral feedings if possible or total parenteral nutrition

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Lactulose.

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Grades III-IV. A

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Seizures. , -

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Table 5. Grades of Encephalopathy

I	Changes in behavior with minimal change in level of consciousness
II	Gross disorientation, drowsiness, possibly asterixis, inappropriate behavior
III	Marked confusion, incoherent speech, sleeping most of the time but arousable to vocal stimuli
IV	Comatose, unresponsive to pain, decorticate or decerebrate posturing

Note: some patients will overlap grades; clinical judgment is required. Adapted from Conn HO, Leevy CM, Vhlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, Levy LL. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. Gastroenterology 1977; 72:573–583.

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A F -
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.[82] A
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.[83] F
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Intracranial Pressure Monitoring

C A F
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13 1998-
2000[84]; 20
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(C ,) ;

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C .[86-89] A -
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C (C ;
C)
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.[90]
A , C / C
.[90,91] C A F -
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C C
,[92]

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C
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,[94]
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262 . . -
3.8% (1%)
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.[95]
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, C -
.[96] ,
(2/58).[97]
C
.[97]

Specific Treatment of Elevated Intracranial Pressure. C -

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C 20-25 -
, C 50-60 .[4,98] E -
C 70 -
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.[99]
C .
Mannitol. C , C
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.[101] A -
(0.5-1 /)
C A F.
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320 / .
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Hyperventilation. C $_2$ 25-30 C - (CBF), - .[102] A F, - CBF .[103] - CBF - - C ; C - , .A A F - / C , - .[104]

.[105] B , A F. - C , - C ; - .

Hypertonic Sodium Chloride. A 30% - 145-155 A F C .[106] - .

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Barbiturate. B (-) C ; C . , - - (A).[107]

Corticosteroids. C , C - , A F .[101]

Hypothermia. (32-34 C) C A F. ,[108-110] - , - , .

- A F ,[111,112] . , , .[113]

Recommendations

25. In early stages of encephalopathy, sedation should be avoided if possible. Lactulose may be used, but concern has been raised about increasing bowel distention during the subsequent transplant procedure (II-2, III).

26. In patients progressing to grade III or IV encephalopathy, the head should be elevated to 30 degrees, and endotracheal intubation should be performed (III).

27. Seizure activity should be treated with phenytoin and low-dose benzodiazepines. (III).

28. Although there is no consensus among the centers and experts, intracranial pressure monitoring is mainly considered for patients who are listed for transplantation (III).

29. In the absence of ICP monitoring, frequent evaluation for signs of intracranial hypertension are needed to identify early evidence of uncal herniation (III).

30. In the event of intracranial hypertension, mannitol should be given and hyperventilation may be considered in order to temporarily reduce the ICP, but prophylactic use of these interventions is not helpful and therefore not recommended (I).

31. Short-acting barbiturates may be considered for refractory intracranial hypertension (III).

32. Corticosteroids should not be used to control elevated ICP in patients with acute liver failure (I).

Infection

A A F [114] [115] , - . - A F, ,[116,117] . A , - .[116] D - , - , . , (, -

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A F. -
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.[117,118] -
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C ,[119] -
C . ,
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Recommendations

33. Periodic surveillance cultures should be performed to detect bacterial and fungal infections as early as possible and prompt treatment should be initiated accordingly

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.[131-133] -
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,[131,132] - A -
. 2 A F[135] , -
- .[136]
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- . .[137] A -
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.[9,138] E
Recommendation -
36. Patients with ALF in the ICU should receive prophylaxis with H2 blocking agents or PPIs (or sucralfate as a second-line agent) for acid-related gastrointestinal bleeding associated with stress (I, III). , -
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(*e.g.*,
Hemodynamics/Renal Failure C D) ,
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C / - .[139]
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A F , AC
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- A F , AC
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. A F ,
- C .[143]
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50-60 A F.
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A F C
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.[134] ,

48
.[144-146] D , -
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Recommendations

37. Careful attention must be paid to fluid resuscitation and maintenance of adequate intravascular volume in patients with acute liver failure (III).

38. If dialysis support is needed for acute renal failure, it is recommended that a continuous mode rather than an intermittent mode be used (I).

39. Pulmonary artery catheterization should be considered in a hemodynamically unstable patient to ensure that appropriate volume replacement has occurred (III).

40. Systemic vasopressor support with agents such as epinephrine, norepinephrine, or dopamine but not vasopressin should be used if fluid replacement fails to maintain MAP of 50-60 mm Hg (III, II-1).

Metabolic Concerns

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[149]
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Recommendation

41. Metabolic homeostasis must be carefully maintained in patients with acute liver failure. Overall nutritional status as well as glucose, phosphate, potassium and magnesium levels should be monitored frequently, with expeditious correction of derangements (III).

Transplantation and Prognosis

Transplantation

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15% - ≥60%
.[5] A

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40%,[5] -
15% - . -
A F
80% 90%,[5,93] -
. . . , 29%
, 10%
(1/4)
.[5]
40%,[150,151]
A F
(1) . D -
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Recommendation

42. Urgent hepatic transplantation is indicated in acute liver failure where prognostic indicators suggest a high likelihood of death (II-3).

Liver Support Systems

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A F.[156] A

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Recommendation

43. Currently available liver support systems are not recommended outside of clinical trials; their future in the management of acute liver failure remains unclear (I, II-1).

Prognosis

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A F.[9]

70% 100%

25%

94%.[161-165] ,

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82% 98%,[166]

Table 6. Potentially Helpful Indicators* of Poor (Transplant-free) Prognosis in Patients With ALF

Etiology
Idiosyncratic drug injury
Acute hepatitis B (and other non-hepatitis A viral infections)
Autoimmune hepatitis
Mushroom poisoning
Wilson disease
Budd-Chiari syndrome
Indeterminate cause
Coma grade on admission
III
IV
King's College Criteria:
Acetaminophen-induced ALF:
Arterial pH <7.3 (following adequate volume resuscitation) irrespective of coma grade OR
PT >100 seconds (INR · 6.5) + serum creatinine >300 μmol/L (3.4 mg/dL) in patients in grade III/IV coma
Non-acetaminophen-induced ALF:
PT >100 seconds irrespective of coma grade OR
Any three of the following, irrespective of coma grade:
– Drug toxicity, indeterminate cause of ALF
– Age <10 years or >40 years‡
– Jaundice to coma interval >7 days‡
– PT >50 seconds (INR ≥3.5)
– Serum bilirubin >300 μmol/L (17.5 mg/dL)

*Please note: None of these factors, with the exception of Wilson disease and possibly mushroom poisoning, are either necessary or sufficient to indicate the need for immediate liver transplantation.

‡These criteria, in particular, have not been found to be predictive of outcome in recent analyses.[5]

[167] -

A F[165]

' C -

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- , B .[168]

A F

, ' C -

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( ),

A C E

(A AC E) [169] (D -

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[170]). ' C

<7.30

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C

(69% 57%),

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A AC E >15

92% (' C -

) 81%,

.[169]

A F,[9,171] . . - A F .[5]

.

A F, A F , A, , - ≥50% , <25% - .

- ,[117,118] A (AF) - ,[172] ,[173] ,[174] C ,[174,175] - ,[176] ,[163,177] - .[178] E ; , . E - D (E D) , - -

,[179] A F, .

Recommendation

44. Currently available prognostic scoring systems do not adequately predict outcome and determine candidacy for liver transplantation. Reliance entirely upon these guidelines is thus not recommended. (II-2, II-3, III).

Summary

A F - .

- . B - , - A F .

Acknowledgment: C AA D . C . , D, C , B . B , D, C. B , D, A C , D, , - . C , ., D, . C , D, - . D , D, E. E , D, . F , D, . F , D, . , D, E , , AC , . , D, . , D, D . , D, F. F , D, C. , D, , B A. , D, . , D, , . , D. *Disclosure Statement:* .

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