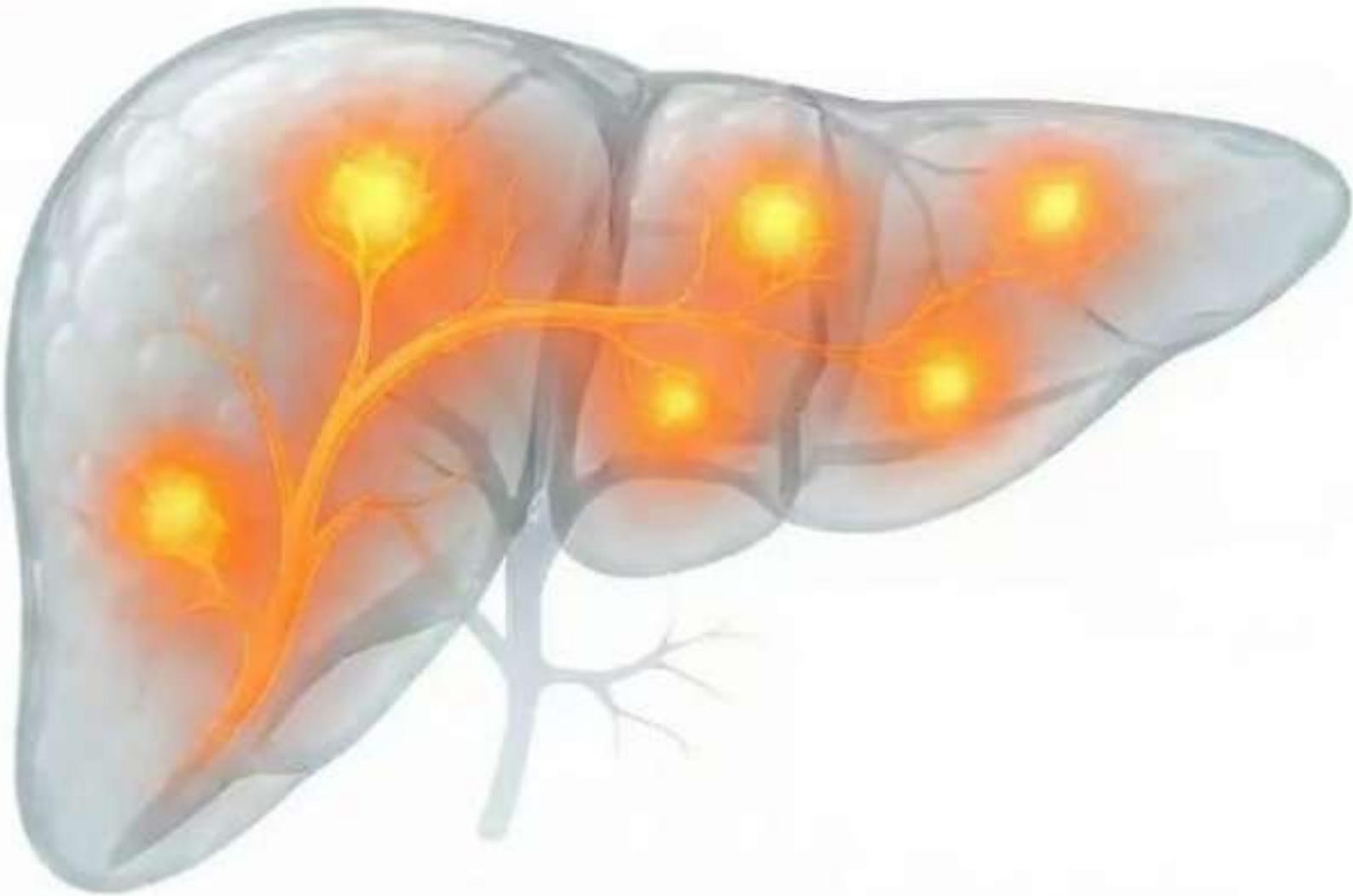
ACUTE LIVER FAILURE

National Standard Treatment Guideline



Ministry of Health
Republic of Maldives

ADB

JFPR
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World Health Organization
Maldives

National Standard Treatment Guidelines

- Acid Peptic Disease
- Acute Anxiety
- Acute Pancreatitis
- Acute Psychosis
- Acute kidney Injury
- Arrhythmia
- Chronic Liver Disease
- Chronic Pancreatitis
- Chronic kidney disease
- Congenital Heart Diseases
- Dementia
- Depression
- Diabetes Mellitus Type 1
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- Gestational Diabetes
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- Hyponatremia
- Hypernatremia
- Hypokalemia
- Hyperkalemia
- Interstitial Lung Disease
- Liver Failure
- Obesity
- Obstructive Sleep Apnoea
- Osteoarthritis
- Ovarian Cancer
- Pneumonia
- Stroke
- Upper Gastrointestinal bleed
- Unstable Angina

Version No	Version Date	Description of change
1	8 November 2025	Initial release

DOCUMENT NUMBER: MOH-QA/G/25/233-0

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Published by

Quality Assurance and Regulations Division
Ministry of Health, Male,
Republic of Maldives

GUIDELINES DEVELOPMENT METHODOLOGY

The development of the Maldives Standard Treatment Guidelines (STGs) followed a structured, evidence-informed, and consensus-driven methodology adapted from internationally accepted guideline-development standards and the Delhi Society for Promotion of Rational Use of Drugs (DSPRUD) model. The process combined systematic evidence retrieval, critical appraisal, contextual adaptation, and multidisciplinary expert review to ensure feasibility, clinical relevance, and national ownership.

1. Determining Scope and Priority Conditions

Priority clinical conditions were identified through consultation with national programme managers, specialty clinicians, and health-system stakeholders. Selection criteria included: (i) major causes of morbidity and mortality, (ii) observed variation in clinical practice or prescribing patterns, (iii) potential to improve patient outcomes, and (iv) the feasibility of implementation across health-facility levels in Maldives. The final list of diseases reflected national epidemiology, service-delivery capacity, and essential-medicine availability.

2. Identification of Existing Evidence and Source Guidelines

A targeted search strategy was used to identify high-quality existing clinical guidelines. Searches were conducted across international guideline repositories (e.g., WHO, NICE, SIGN and other intergovernmental bodies, international and national guideline repositories, specialty societies and professional associations.

3. Quality Appraisal of Source Guidelines

Retrieved guidelines were screened for transparency of development, methodological rigour, clarity of recommendations, applicability to health-system reality, editorial independence. Guidelines were included if they met the Institute of Medicine (IOM) definition of a clinical guideline and addressed treatment or management of priority conditions. Guidelines that did not meet minimum quality standards, review articles, diagnostic criteria, or technical standards were excluded.

4. Adoption, Adaptation, and Contextualization

The guideline-development team employed an adopt–adapt–contextualize model:

- **Adoption**: High-quality recommendations that aligned with Maldivian health-system realities were retained without modification.
- **Adaptation**: Recommendations were modified when local considerations such as diagnostic capacity, medicine availability, workforce skills, referral pathways, or cost constraints affected feasibility.

- **Contextualization**: Where evidence was absent or inconclusive, conditional recommendations were formulated based on expert consensus, with explicit consideration of pragmatism, safety, and local workflows.
  Medicines were selected in alignment with the Maldives National Essential Medicines List (NEML), based on suitability, efficacy, safety, and availability.

5. Expert Consensus and Multidisciplinary Input

Draft recommendations were initially prepared by experts from the DSPRUD, India, providing a strong methodological foundation for the process. Building on this, a collaborative and participatory process brought together clinicians from internal medicine, paediatrics, obstetrics-gynaecology, surgery, emergency medicine, endocrinology, cardiology, general practitioners, and public health representing different levels of healthcare. Consensus was achieved through moderated discussions, iterative revisions, and resolution of divergent views. For topics lacking strong evidence, recommendations were derived from expert clinical judgment grounded in extensive practice experience.

6. Drafting, Peer Review, and Validation

Each guideline section was organized in a standard format including key clinical features, essential investigations, non-pharmacological management, pharmacological therapy (with step-up/step-down options where relevant), referral criteria, paediatric considerations, and follow-up requirements. Drafts were peer-reviewed by senior clinicians and national experts. Reviewer comments were systematically integrated to strengthen clarity, accuracy, and applicability.

7. Addressing Conflicts of Interest

All contributors declared the absence of conflicts of interest. Individuals with potential or perceived conflicts were excluded from authorship or decision-making roles.

8. Updating and Future Revisions

The STGs were conceptualized as a living document. Future updates will incorporate new scientific evidence, changes in essential-medicine availability, national programme priorities, and user feedback from clinicians. Periodic review cycles will ensure the continued relevance and reliability of recommendations.

9. Distinctive Features of the Guidelines

Developed through a collaborative process involving a large group of multidisciplinary experts from different levels of healthcare, the guidelines incorporate the following distinctive features:

- **Diagnostic Assumption and Confirmation**: While assuming that an initial diagnosis has been established by the healthcare provider, the guidelines provide essential information for confirming diagnoses. This includes a comprehensive overview of major signs and symptoms, descriptions of confirmatory tests, and clear guidance on practices that are prohibited, discouraged, or unreliable—promoting evidence-based medicine supported by relevant references.
- **Comprehensive Treatment Approach**: The guidelines offer a systematic, up-to-date framework for managing medical conditions across the continuum of care. They begin at the primary care level and extend to secondary and tertiary care, incorporating protocols for treatment response assessment and referral criteria as integral components.
- **Diverse Treatment Modalities**: Recommendations encompass both non-pharmacological and pharmacological interventions and surgical intervention where applicable, providing flexibility for individualized treatment plans. Cautionary notes are included where necessary to ensure safe and effective use of therapies.
- **Assessment and Referral Criteria**: Clear criteria and goals for evaluating patient response to treatment are provided, along with guidance on when referral to higher levels of care is warranted ensuring continuity and comprehensiveness in patient management.

ACKNOWLEDGEMENTS

The Government of the Republic of Maldives is committed to ensuring universal access to quality health services for all citizens. The Constitution of Maldives mandates the progressive realization of rights, including the right to good standards of health care for the population. In line with this national commitment, standardized quality health services are regarded as the foundation of a strong and equitable healthcare system.

This important work would not have been possible without the cooperation and support of many individuals and institutions. We express our sincere appreciation to the Honourable Minister of Health, Abdullah Nazim Ibrahim, for his leadership, commitment, and continuous guidance throughout the development process. We are grateful to WHO and ADB for their significant contribution, support, and technical assistance.

Our heartfelt gratitude is extended to the technical lead and editor, Dr. Sangeeta Sharma, Professor, Neuropsychopharmacology, IHBAS and President, Delhi Society for Promotion of Rational Use of Drugs (DSPRUD), and her team. We express our deepest appreciation to the Maldivian and DSPRUD experts and contributors who played a pivotal role in this process. Their technical expertise and dedication to adapt the standards to the Maldivian context have been instrumental in the development and finalization of these guidelines. The time, experience, generous sharing of knowledge and insights contributed by all parties have not only enriched the work but also have been invaluable in making these standards practical, locally acceptable, and aligned with the needs of the resident population.

It is important to acknowledge the immense efforts, involvement, timely coordination, collaboration, and dedication of the Quality Assurance and Regulation Division team who made it possible for these Clinical Treatment Guidelines to come into existence.

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ACUTE LIVER FAILURE

QUICK REFERENCE GUIDE

Acute liver failure (ALF) is relatively uncommon but carries high mortality, with overall transplant-free survival around 50% and mortality historically exceeding 60% without modern ICU care. It affects all adult age groups but shows worse prognosis in young (<10) or >40 years old and in pregnancy, especially with HEV infection. Morbidity is driven by rapid multi-organ dysfunction (cerebral edema, renal failure), and sepsis are frequent complications. Outcomes vary by etiology: acetaminophen-related ALF often has better recovery with timely N-acetylcysteine, while Wilson disease and pregnancy-related cases have poor spontaneous survival, making early transplant referral critical.

Definition

Acute liver failure (ALF) refers to sudden liver damage in individuals without pre-existing chronic liver disease. It is characterized by coagulopathy (international normalized ratio INR ≥1.5) and any hepatic encephalopathy (HE) within ≤26 weeks of symptom onset. If encephalopathy is absent, the condition is called acute liver injury (ALI). The clinical course is classified by timing. Time-based course is either hyperacute (jaundice to HE ≤7 days), Acute (8-28 days), Subacute (5-12 weeks).

Causes, risk factors & triggers

- **Causes:** Acetaminophen toxicity; viral hepatitis A/B/E (rarely C; hepatitis B virus HBV reactivation); idiosyncratic drug-induced liver injury (DILI); autoimmune hepatitis; ischemic hepatitis; Wilson disease; pregnancy-related (acute fatty liver of pregnancy/ HELLP); toxins (e.g., Amanita).
- **Risk factors**: Overdose or staggered acetaminophen use, alcohol use disorder, malnutrition, pregnancy (HEV), immunosuppression (HBV reactivation).
- **Common triggers:** Sepsis, hypotension/arrhythmia, new hepatotoxic drugs/herbals, heatstroke.

Evaluation for diagnosis

- **Clinical features:** Prodrome (fatigue, anorexia, nausea, right upper quadrant pain), rapid jaundice, coagulopathy, encephalopathy.
- **Examination:** Icterus, tender hepatomegaly, fever, tachycardia, hypotension; signs of cerebral edema (altered pupils, posturing).
- **Laboratory investigations:** Complete blood count, comprehensive metabolic panel, AST/ALT (aspartate/alanine aminotransferases), bilirubin, INR/PT, fibrinogen, ammonia, glucose, lactate, arterial/venous blood gas, pregnancy test.

- **Etiology panel (draw early):** Acetaminophen level (repeat at 4 h if timing unclear); HAV IgM, HBsAg ± HBV DNA, HCV RNA, HEV IgM; autoimmune markers (ANA/ASMA/IgG); toxicology; Wilson workup (ceruloplasmin, hemolysis labs, 24-h urinary copper).
- **Imaging:** Right upper quadrant ultrasound with Doppler to exclude obstruction and assess hepatic/portal flow; CT brain without contrast for HE grade ≥3 or focal signs.

Confirmation of diagnosis

- No prior cirrhosis + INR ≥1.5 + any HE = ALF. If HE absent - ALI.

Staging/severity assessment criteria

- **Encephalopathy (West Haven):** I-IV (mild inattention to coma).
- **King's College Criteria (KCC):** Poor-prognosis triggers (different for acetaminophen vs non-acetaminophen).
- **Lactate (acetaminophen):**>3.5 mmol/L at 4 h or >3.0 mmol/L at 12 h despite resuscitation = adverse.
- **Ammonia:**>150-200 µmol/L higher cerebral edema risk.
- **Model for End-Stage Liver Disease-sodium (MELD-Na)/MELD 3.0:** Supports risk; does not replace KCC.

Differential Diagnosis (conditions that mimic ALF)

- Acute-on-chronic liver failure (ACLF), decompensated cirrhosis, sepsis-associated cholestasis, ischemic hepatitis, obstructive cholestasis (choledocholithiasis), anticoagulant effect or vitamin K deficiency, disseminated intravascular coagulation, uremic or metabolic encephalopathy, intracranial events.

Management goals & principles

- Stabilize airway, breathing, circulation (ABCs).
- Treat the cause immediately (do not wait for full confirmation).
- Protect brain (limit intracranial pressure), support kidneys and hemodynamics, prevent/treat infection.
- Reassess frequently; call transplant center early if poor-prognosis criteria or no improvement ≤72 h.

Approach to management

1. **Triage (first 30 min):** Oxygen, IV access, glucose; labs and cultures; ICU admission.
2. **Airway:** Intubate for HE ≥III or unsafe airway; target $PaCO_2$ 35-40 mmHg.
3. **Circulation:** Balanced crystalloids; target mean arterial pressure (MAP) ≥65 mmHg with norepinephrine (add vasopressin if needed).

4. **Cause-directed therapy:** Start N-acetylcysteine (NAC) in all suspected acetaminophen/indeterminate ALF; etiology-specific antivirals; steroids for autoimmune hepatitis if infection excluded.
5. **Brain protection:** Head-up 30°, hypertonic saline (aim Na 145-150 mEq/L) or mannitol for spikes; consider continuous renal replacement therapy (CRRT) to lower ammonia.
6. **Renal/metabolic:** Hourly urine/glucose early; start CRRT for acute kidney injury (AKI), severe hyperammonemia, acidosis, or overload; correct electrolytes.
7. **Coagulation**: Avoid routine fresh frozen plasma/platelets; give vitamin K if deficiency likely; transfuse only for bleeding/procedure.
8. **Infection control:** Low threshold for empiric antibiotics when sepsis suspected; de-escalate to cultures.
9. **Prognosis/transfer:** Apply KCC (± Clichy/lactate) repeatedly; engage transplant team early.

Non-pharmacological interventions

- **Early tele-hepatology** if no onsite transplant services.
- **Standard bundles:** ALF recognition checklist (INR, AST/ALT, ammonia, mental status).
- **Low-resource setting:** Prioritize NAC, balanced fluids, infection control, ultrasound with Doppler, timely transfer; avoid hepatotoxins and unnecessary sedatives; use checklists to prevent delays.

Pharmacological therapy

- **N-acetylcysteine (NAC), IV (5% dextrose):** 150 mg/kg over 1 h followed by 50 mg/kg over 4 h then 100 mg/kg over 16 h (cap weight at 100 kg). Extend (e.g., 6.25 mg/kg/h) if INR/ALT not improving or acetaminophen detectable. Watch for anaphylactoid reactions; administer at slow rate/ antihistamine.
- **Activated charcoal (oral/NG):** 1 g/kg (max 50 g) within ≤4 h of ingestion if airway protected; consider multi-dose for amatoxin or sustained-release drugs.
- **HBV antivirals:** Tenofovir disoproxil fumarate 300 mg orally daily (or entecavir 0.5-1 mg orally daily), start after drawing HBV DNA; adjust for renal function.
- **Herpes viruses:** Acyclovir 10 mg/kg IV q8h (renal adjust) for suspected herpes simplex/varicella zoster hepatitis; ganciclovir 5 mg/kg IV q12h for cytomegalovirus (monitor cytopenias).
- **Autoimmune hepatitis:** Methylprednisolone 1-2 mg/kg/day IV (or prednisolone 40-60 mg/day orally) after excluding sepsis; reassess at 48-72 h.

- **Amanita phalloides:** Silibinin IV 20-50 mg/kg/day (where available) ± high-dose penicillin G; give NAC; early transplant discussion.
- **Budd-Chiari (hepatic vein thrombosis): Enoxaparin 1 mg/kg subcutaneous** q12h (renal adjust); consider transjugular intrahepatic portosystemic shunt (TIPS) if severe.
- **Antibiotics/antifungals:** Start broad if sepsis suspected; narrow to cultures; avoid nephrotoxins when possible; monitor levels (e.g., vancomycin).

Assessment of response, review & treatment adjustment

- **Monitor trends:** Neurologic grade, INR, bilirubin, ammonia, lactate, creatinine/ urine output, AST/ALT, MAP.
- **Positive response:** Improving mentation, falling INR/bilirubin/lactate/ ammonia, stable hemodynamics, recovering renal function.
- **If no improvement in 24-72 h or deterioration:** Step-up care (airway, vasopressors, CRRT, hypertonic therapy), re-apply KCC, and activate transplant pathway.
- **De-escalate:** Narrow antibiotics, taper hypertonic therapy carefully (avoid rapid sodium drop), wean CRRT/ pressors when stable; stop NAC when INR/enzymes clearly improve or transplant occurs.

Referral linkages

- **Primary/secondary hospitals:** Stabilize, start NAC, send etiologic labs, arrange early teleconsultation and transfer if KCC met, MELD-Na rising, HE ≥III, ammonia >150-200 µmol/L, pH <7.30, INR ≥6.5, refractory shock, or no improvement ≤72 h.
- **Tertiary/transplant centers:** Full etiologic workup, invasive monitoring as needed, organ support (ventilation, CRRT), and urgent transplant evaluation/listing.

Complications (recognize early; manage aggressively)

- **Cerebral edema/intracranial hypertension**: Ammonia-driven; target ICP <25 mmHg, cerebral perfusion pressure CPP >50 mmHg if monitored; use hypertonic saline/mannitol, controlled ventilation, CRRT.
- **AKI/renal failure:** Prefer CRRT in unstable patients.
- **Shock/sepsis:** Early antimicrobials, source control, norepinephrine.
- **Coagulopathy:** Transfuse only for procedures/bleeding; vitamin K if deficiency.
- **Respiratory failure/acute respiratory distress syndrome (ARDS):** Lung-protective ventilation; aspiration prevention.
- **Metabolic:** Continuous dextrose for hypoglycemia; correct electrolytes; treat severe acidosis.

Patient education & caregiver instructions

- **Act now:** ALF is an emergency; transplant may be needed on short notice.
- **Do:** Stay reachable; provide exact ingestion/drug history; consent to transfer/teleconsultation; report new confusion, drowsiness, bleeding, fever, or reduced urine.
- **Don't:** Give any non-approved medicines, alcohol, or supplements; do not leave against medical advice.
- **After discharge (if not transplanted):** No alcohol; avoid unapproved drugs/ herbals; attend all follow-ups; **If confusion or excessive sleepiness appears with jaundice- treat it as an emergency and return urgently**.

INTRODUCTION

Liver failure is either acute defined by sudden coagulopathy (international normalized ratio ≥1.5) with any encephalopathy in a person without prior chronic liver disease or chronic, which progresses over years, usually on the background of cirrhosis. Acute liver failure (ALF) most often follows viral hepatitis, drug-induced injury such as paracetamol overdose, toxins, or tropical infections, and presents with jaundice, coagulopathy, and encephalopathy; it is uncommon but highly lethal without protocol-based care. Chronic liver failure (CLF) stems mainly from chronic hepatitis B and C, alcohol-related liver disease, and metabolic dysfunction-associated steatotic liver disease (MASLD), remaining compensated for years before decompensating with ascites, variceal bleeding, jaundice, or encephalopathy. In the South-East Asia Region, viral hepatitis drives much of both acute and chronic disease, with very large HBV/HCV pools; dengue and other infections also contribute to acute presentations. Management differs between acute and chronic failure but shares core principles: early recognition, cause-directed therapy, standardized protocols (including acute-on-chronic pathways), and timely referral, which together improve survival and support training, audit, and equitable care.

SCOPE OF THIS GUIDELINE

This guideline addresses primarily ALF It covers adult patients (≥ 18 years) presenting with rapid loss of hepatic function, coagulopathy and any encephalopathy within days to weeks. Covers early diagnosis, etiology-directed therapy, organ support, referral triggers, and step-up/step-down plans. Excludes pediatrics ALF where definitions and causes are different.

Intended users

This document is intended for clinicians in secondary and tertiary care, hepatologists, intensivists, gastroenterologists, transplant teams and allied professionals who manage ALF.

Applicability by level

- **Primary care/ER (no ICU):** Spot ALF (INR ≥ 1.5 + any encephalopathy), basic labs, treat hypoglycemia, stop hepatotoxins, start N-acetylcysteine if suspected, stabilize ABCs, same-day transfer.
- **Secondary care (district/HDU):** Confirm etiology (viral tests, ultrasound), start specific therapy, prevent complications, manage fluids/vasopressors, transfer if grade ≥ 2 HE, AKI, shock, or transplant criteria met.

- **Tertiary care (ICU/transplant):** Comprehensive workup, targeted organ support (airway/ICP/CRRT), definitive therapy, early transplant assessment; standardized bundles and daily review.

For those areas, refer to dedicated pediatric, obstetric, metabolic and transplant-specific guidelines. This will focus on ALF related management issues. Management issues of CLF and ACLF are not discussed in these guidelines.

DEFINITIONS

Acute Liver Failure (ALF): ALF is acute liver injury in a patient without pre-existing chronic liver disease/cirrhosis, characterized by coagulopathy (international normalized ratio ≥1.5) and any degree of hepatic encephalopathy, usually within 26 weeks of symptom onset. If encephalopathy is absent, the condition is termed acute liver injury (ALI), not ALF. (AASLD)

Acute-on-Chronic Liver Failure (ACLF)

ACLF describes an acute deterioration of liver function in patients with underlying chronic liver disease or cirrhosis, precipitated by a distinct insult (e.g., infection, alcohol binge, drug toxicity), and accompanied by failure of the liver and one or more extrahepatic organ systems.

APASL (Asian Pacific Association for the Study of the Liver): ACLF is defined as "an acute hepatic insult manifesting as jaundice (serum bilirubin ≥5 mg/dL) and coagulopathy (INR ≥1.5 or prothrombin activity <40%), complicated within 4 weeks by clinically detectable ascites and/or hepatic encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease, and associated with high 28-day mortality."

EASL (European Association for the Study of the Liver): ACLF is defined as "acute decompensation of cirrhosis, associated with organ failure(s) and high short-term mortality, usually triggered by a precipitating event." Diagnosis is based on the CLIF-C (Chronic Liver Failure Consortium) **CLIF-C OF/CLIF-C ACLF** scores, which use the CLIF-SOFA score to assess the number and type of organ failures and stratify mortality risk.

RISK FACTORS & TRIGGERS ACUTE LIVER FAILURE

Etiology	Mechanism / Type	Key Triggers & Risk Factors	Usual Presentation / Labs	Prognosis
Drug-induced liver injury (DILI)	Intrinsic (predictable, dose-dependent) or idiosyncratic (rare, unpredictable)	Acetaminophen (paracetamol) single or chronic overdose; risk increases with dose >7.5 g/day, alcohol use disorder, malnutrition. Idiosyncratic: antibiotics, antitubercular drugs (isoniazid, rifampicin, pyrazinamide), anticonvulsants, halothane, herbal/dietary supplements	Jaundice, malaise; marked aminotransferase rise (often AST/ALT >1000 IU/L in acetaminophen), coagulopathy	Leading cause of ALF in many high-income countries
Viral hepatitis (A, B, E; rarely C)	Acute viral cytopathic injury; HBV reactivation with immunosuppression	Endemic exposure (South/ Southeast Asia), pregnancy (HEV highest risk), lack of vaccination	Acute hepatitis with jaundice, raised ALT/AST, INR rise; HEV in pregnancy can progress rapidly	HEV-related ALF in pregnancy: mortality up to ~70%.
Toxins (e.g., Amanita phalloides amatoxin)	Potent RNA polymerase II inhibition leading to massive hepatocyte necrosis	Mushroom ingestion (foraged/unknown species)	Severe vomiting/diarrhea, latent phase - fulminant hepatic failure; very high transaminases, raised INR	Urgent referral
Metabolic (Wilson disease)	Copper accumulation; hemolysis + hepatic failure	Young adults/teens; low ceruloplasmin, Coombs-negative hemolysis	Acute hemolysis, low alkaline phosphatase, high bilirubin; Kayser-Fleischer rings	Poor response to medical therapy in ALF
Ischemic hepatitis ("shock liver")	Hypoperfusion or hypoxia; hepatic congestion/necrosis	Shock, cardiac arrest, severe heart failure, drastic hypotension; vascular: Budd-Chiari, sinusoidal obstruction (veno-occlusive disease)	Abrupt AST/ALT surge (>2000 IU/L), lactate ↑, modest bilirubin early	Treat underlying hemodynamic insult; anticoagulate Budd-Chiari
Autoimmune hepatitis flare	Immune-mediated hepatocyte injury	Known or new AIH; precipitated by drug/ infection	Hypergammaglobulinemia, positive ANA/ASMA, interface hepatitis (biopsy)	
Pregnancy-related	Micro-vesicular steatosis/HELLP or viral HEV	3rd trimester/post-partum; preeclampsia	Hypoglycemia, ↑ammonia, coagulopathy; hemolysis, elevated liver enzymes, low platelets	Obstetric emergency
Heatstroke, severe sepsis, malignancy infiltration	Hyperthermia-induced hepatocellular injury; inflammatory/ ischemic; tumoral replacement	Environmental exposure; advanced cancer	Mixed cholestatic/ hepatocellular pattern; systemic features	

EVALUATION FOR DIAGNOSIS

Component	What to check	Findings that favor ALF	Key thresholds
Symptoms & clinical clues	Fatigue, anorexia, nausea/ vomiting, right-upper-quadrant discomfort; time course from jaundice to altered mentation	Rapid progression over days from prodrome to jaundice to coagulopathy to encephalopathy	Sudden course (days-weeks) in a patient without pre-existing cirrhosis
Neurologic status (West Haven)	Mental status, attention, sleep-wake cycle, asterixis	Any encephalopathy: irritability, asterixis, disorientation, somnolence, coma	Grades I-IV; presence of any grade with INR ≥1.5 = ALF
Symptoms & General examination clues	Icterus, hepatomegaly/ tender liver; fever; volume status	Icterus common; tender hepatopathy; fever, tachycardia, hypotension suggest SIRS/sepsis	Rapid worsening of encephalopathy + synthetic failure = emergency
Hemodynamics & renal	Blood pressure, heart rate, urine output, creatinine	Hypotension/tachycardia, oliguria, rising creatinine	Consider early vasopressors; evaluate for hepatorenal/ischemic injury
Coagulation	INR, bleeding signs	Coagulopathy with mucosal/GI bleed	INR ≥1.5 defines impaired synthetic function (core ALF criterion)
Aminotransferases	AST, ALT trends	Marked elevation; often AST/ALT >1000 IU/L	≥3000 IU/L usually seen in acetaminophen or ischemic injury
Pattern suggesting idiosyncratic DILI	ALT with INR	ALT >10× ULN plus INR ≥1.5 supports ALF from DILI	ULN example: ALT >350 IU/ L if ULN 35
Ammonia	Arterial ammonia	Correlates with cerebral edema risk	>100 µmol/L risk; >200 µmol/L poor outcome
Lactate	Arterial lactate at 4-12 h	Prognostic in acetaminophen ALF	>3.5 mmol/L (4 h) or >3.0 mmol/L (12 h) - worse prognosis
Etiology workup (draw early)	Acetaminophen level (repeat at 4 h if unknown timing); viral markers (HAV IgM, HBsAg/HBeAg/HBV DNA, anti-HCV/HCV RNA, HEV IgM), autoimmune panel (ANA/ASMA/IgG), pregnancy test, tox screen, Wilson workup (ceruloplasmin, hemolysis, 24-h urinary copper), blood/urine cultures	Identifies treatable causes (e.g., NAC for acetaminophen, antivirals for HBV, steroids for autoimmune)	Start N-acetylcysteine while evaluating when ALF suspected
Imaging	Ultrasound with Doppler	Exclude biliary obstruction; assess hepatic/portal flow (Budd-Chiari), look for edema	CT/MRI if diagnosis unclear or to assess complications

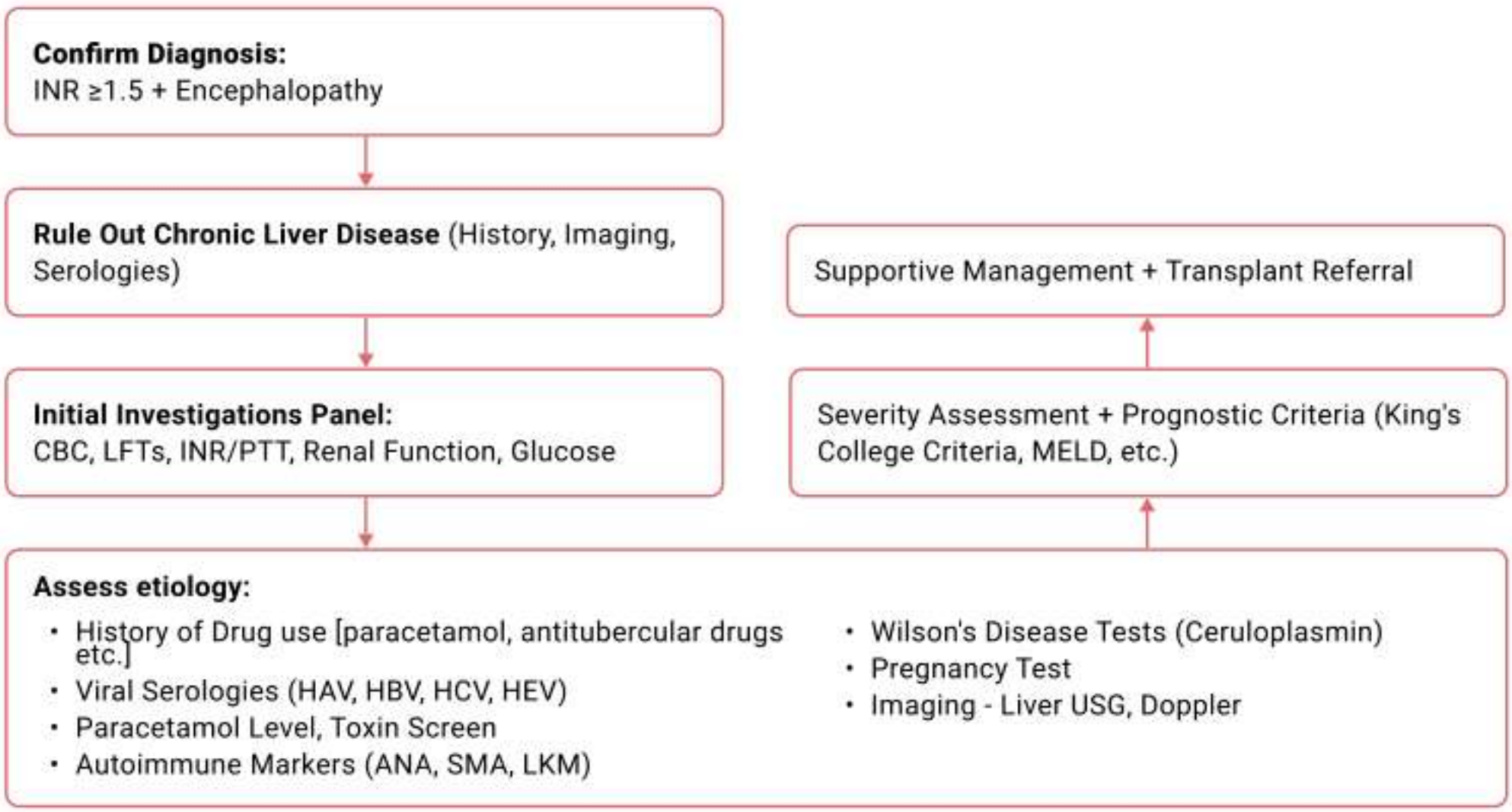
West Haven Grades of Hepatic Encephalopathy	
Grade 1	Inverted sleep pattern; forgetfulness, agitation, irritability, apraxia
Grade 2	Lethargy; disorientation for time or place, Subtle personality change; Asterixis, ataxia
Grade 3	Somnolence but arousability, Disorientation as regards place; Asterixis, hyperactive reflexes, Babinski signs, muscle rigidity
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

Diagonosis

Suspect ALF in any patient with acute hepatitis signs plus INR ≥ 1.5 and altered mentation. Admit immediately to ICU for comprehensive evaluation. Initial workup includes:

- Prothrombin time/INR, AST/ALT, bilirubin, albumin
- Ammonia, lactate, arterial blood gas
- Renal panel, glucose, electrolytes
- Viral serologies (HAV, HBV, HEV), autoimmune markers (ANA, ASMA), ceruloplasmin
- Toxicology screen, acetaminophen (paracetamol) level
- Abdominal ultrasound to exclude vascular causes

Suspected Acute Liver Failure



CONFIRMATION OF DIAGNOSIS: ALF

Must have (all three)

1. **No pre-existing chronic liver disease**. History, exam, and ultrasound should not suggest cirrhosis or portal hypertension.
2. **Acute time course:** illness duration ≤26 weeks from symptom onset.
3. **Coagulopathy + encephalopathy:** INR ≥1.5 (not due to anticoagulants, not corrected by vitamin K) and any hepatic encephalopathy (West Haven I-IV).

If encephalopathy absent

- Term is acute liver injury (ALI), not ALF, even with INR ≥1.5. Monitor closely for the progression to HE, reclassified as ALF.

Supportive (strengthening the diagnosis, assess severity)

- Marked aminotransferases: AST/ALT often >1,000 IU/L; ≥3,000 IU/L usually seen in acetaminophen or ischemic injury.
- Hyperbilirubinemia (especially in viral/immune causes).
- Arterial ammonia >100 µmol/L (risk of cerebral edema).
- Factor V <20-30% (where available) supports impaired synthesis

DIFFERENTIAL DIAGNOSIS: ALF

Condition	Why it looks like ALF	Clues against de novo ALF	Key tests to differentiate	Initial management / pitfalls
Acute-on-chronic liver failure (ACLF)	Jaundice, coagulopathy, encephalopathy after an acute insult (infection, alcohol, bleed)	Stigmata of cirrhosis (spider nevi, splenomegaly), nodular/shrunken liver, portal hypertension, long history	Ultrasound with Doppler; platelets (low), elastography; prior records; CLIF-C scores	Treat precipitant, organ support, early transplant discussion via ACLF pathways (not ALF criteria)
Ischemic hepatitis ("shock liver")	Dramatic AST/ALT spike; encephalopathy in severe shock	Clear hypotension/ arrhythmia/sepsis preceding enzyme rise; lactate very high; bilirubin modest early	Lactate, troponin, echocardiography; hemodynamic chart review	Fix perfusion first (fluids/vasopressors); enzymes fall rapidly if corrected; transplant rarely needed

Acute biliary obstruction (e.g., choledocholithiasis; gallstone ileus)	Jaundice, abdominal pain; may have confusion if septic	Cholestatic pattern (ALP/GGT >> ALT); ductal dilation; colicky pain/fever	RUQ on ultrasound - duct dilation; MRCP/ ERCP as needed; blood cultures if cholangitis	Urgent ERCP for obstruction; antibiotics for cholangitis; not ALF unless septic shock causes failure
Sepsis-associated cholestasis	Jaundice, ↑INR, confusion	Clear infection source; bilirubin and ALP rise with modest transaminases; encephalopathy explained by sepsis	Cultures, procalcitonin, infection imaging, lactate	Source control + antibiotics; avoid mislabeling as ALF and unnecessary transplant listing
Metabolic crises (Wilsonian crisis; acute fatty liver of pregnancy/HELLP)	Acute jaundice, coagulopathy, encephalopathy	Wilson: Coombs-negative hemolysis, low alkaline phosphate, young age, KF rings. AFLP/ HELLP: 3rd trimester/ post-partum, hypoglycemia, hemolysis, low platelets	Wilson: ceruloplasmin, hemolysis panel, 24-h urinary copper. AFLP/ HELLP: glucose, ammonia, CBC, OB assessment/US	Wilson: ICU support, urgent transplant often definitive. AFLP/HELLP: stabilize mother and expedite delivery; coordinate OB-ICU early

CLASSIFICATION/SEVERITY ASSESSMENT

A) Classification

- **Time-based (O'Grady/King's College)**
  - **Hyperacute:** jaundice to encephalopathy ≤ 7 days
  - **Acute:** 8-28 days
  - **Subacute:** 5-12 weeks

  Implication: hyperacute forms have more cerebral edema but better transplant-free survival; subacute forms recover spontaneously less often.

- **Japanese (Intractable Hepato-Biliary Diseases Study Group):**
  - **Fulminant: o**nset of encephalopathy within ≤8 weeks of symptoms, subclassified as
    - **Acute:** ≤10 days
    - **Subacute:** 11 days-8 weeks
  - **Late-onset hepatic failure:** 8-24 weeks

    ***Implication*:** distinguishes very rapid "acute" cases from slower "subacute," and separates late-onset due to different outcomes and transplant timing.

- **Etiology-based**
  - **Acetaminophen/ischemic, viral (A, B, E;** ± HBV reactivation), idiosyncratic DILI, autoimmune, Wilson disease, pregnancy-related (AFLP/HELLP), toxins (amatoxin), indeterminate.
    Etiology drives prognosis and treatment (e.g., NAC for acetaminophen).
- **Encephalopathy grade (West Haven)**
  - **I-IV:** from mild inattention/asterixis to coma.
    Grades III-IV signal severe disease and ICU need.

B) Severity assessment (who needs transplant-center care now)

1. **King's College Criteria (most used)**
   - **Acetaminophen ALF**
     - Arterial pH < 7.30 (after resuscitation) OR
     - All three: INR > 6.5, creatinine > 3.4 mg/dL (300 µmol/L), grade III-IV HE - Poor prognosis, need urgent transplant assessment
   - **Non-acetaminophen ALF**
     - INR > 6.5 regardless of HE OR
     - Any 3 of: age <10 or >40, etiology: non-A, non-B hepatitis, idiosyncratic DILI, jaundice to HE >7 days, INR >3.5, bilirubin >17.5 mg/dL (300 µmol/L) has poor prognosis; urgent transplant assessment required.
2. **Clichy (Bernuau) criteria (viral/indeterminate)**
   - Factor V <20% (age >30) or <30% (age <30) plus encephalopathy. Poor prognosis, consider transplant
3. **Lactate criteria (acetaminophen)**
   - Arterial lactate >3.5 mmol/L at 4 h or >3.0 mmol/L at 12 h post-presentation despite resuscitation. Adverse prognosis
4. **Ammonia**
   - Arterial ammonia >100 µmol/L: cerebral edema risk; >200 µmol/L: very poor outcome
5. MELD (Model for End-Stage Liver Disease)Score / MELD-Na

   The original MELD formula of MELD = 3.78 × ln(bilirubin) + 11.2 × ln(INR) + 9.57 × ln(creatinine) + 6.43, with any values less than 1 adjusted to 1 to avoid negative scores. The score ranges from 6 (least severe) to 40 (most severe).

A revised version, known as MELD-Na, incorporates serum sodium to better reflect prognosis, especially in patients with hyponatremia. The MELD-Na formula is: MELD-Na = MELD + 1.32 × (137 – Na) – [0.033 × MELD × (137 – Na)], with sodium levels capped between 125 and 137 mmol/L for calculation.

Implications: *Higher MELD scores indicate higher short-term mortality; used by transplant networks like UNOS to allocate donor livers fairly and is also useful in managing complications of cirrhosis and determining prognosis in other liver-related conditions; supportive for triage but do not replace KCC.*

6. **Organ-failure scores (ICU context)**

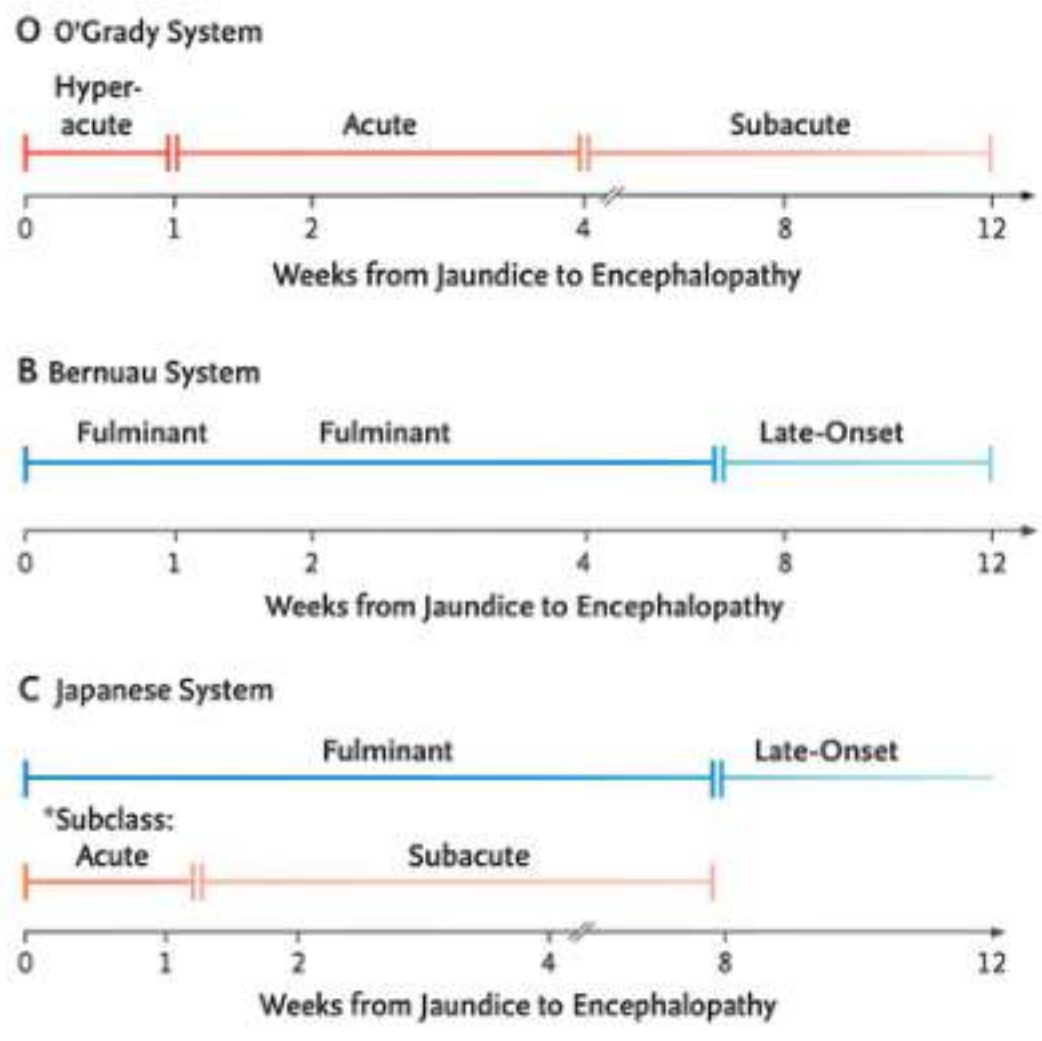
- SOFA and CLIF-OF components help track multiorgan failure; rising scores = worse prognosis.

C) Bedside red flags for "severe ALF"

- HE grades III-IV, INR ≥6.5, bilirubin ≥17.5 mg/dL, creatinine ≥3.4 mg/dL, pH <7.30, lactate above thresholds, ammonia >150-200 µmol/L, hypotension despite fluids, hypoglycemia, progression of HE within hours.

Note

- Classify by time to HE and etiology, grade HE, then apply King's criteria (± Clichy, lactate).
- Any trigger met - immediate transplant-center referral, continue NAC where indicated, and escalate organ support.



MANAGEMENT GOALS IN ALF

The primary objectives in managing acute liver failure focus on life-saving interventions, minimizing complications, and timely evaluation for liver transplantation. These goals should guide all aspects of care, from initial stabilization to definitive treatment.

- Stabilize airway, breathing, and circulation.
- Reverse or halt liver injury by treating the underlying cause (e.g., N-acetylcysteine for paracetamol overdose, antivirals for viral hepatitis, steroids for autoimmune hepatitis).
- Correct coagulopathy (if needed) and acid-base disturbances
- Prevent and manage complications such as cerebral edema, coagulopathy, infection, renal failure, and metabolic derangements.
- Maintain hemodynamic and metabolic stability.
- Identify candidates for urgent liver transplantation and initiate early referral.

MANAGEMENT PRINCIPLES - ACUTE LIVER FAILURE (ALF)

Acute liver failure is a medical emergency requiring multidisciplinary critical care, rapid etiological assessment, and in many cases, early consideration for liver transplantation. All patients should be admitted to an ICU, preferably in a center with liver transplant capability. Management is primarily supportive while addressing the underlying cause.

1. **Immediate Critical Care** - Continuous monitoring of vital signs, neurologic status, urine output, and hemodynamics.
2. **Airway and Ventilation** - Early intubation for Grade III-IV encephalopathy or if airway protection is compromised. Maintain oxygenation and normocapnia.
3. **Hemodynamic Support** - Maintain adequate mean arterial pressure with crystalloids or vasopressors; avoid fluid overload.
4. **Renal Support** - Initiate continuous renal replacement therapy for acute kidney injury or severe hyperammonemia.
5. **Neurological Protection** - Monitor for cerebral edema and raised intracranial pressure; elevate head, maintain normothermia and normoglycemia, avoid hyponatremia. Use mannitol or hypertonic saline if indicated.

6. **Metabolic and Nutritional Management -** Maintain glucose 160-200 mg/dL; correct hypoglycemia promptly. Prefer enteral nutrition; monitor and correct electrolyte and acid-base imbalances.
7. **Medication Review** - Discontinue non-essential home medications; continue only those deemed necessary.
8. **Coagulopathy Management** - Monitor INR and platelet count. Avoid prophylactic plasma or platelet transfusion unless active bleeding or invasive procedure planned.
9. **Infection Control** - Daily clinical assessment with low threshold for cultures; start empiric antibiotics if infection is suspected. Provide stress ulcer and DVT prophylaxis.
10. **Etiology-Specific Therapy** - Initiate targeted treatment immediately (e.g., N-acetylcysteine for paracetamol toxicity, antivirals, corticosteroids) without waiting for full confirmation.
11. **Monitoring and Prognostication -** Frequent neurologic exams; serial labs including LFTs, INR, ammonia, and lactate. Use prognostic tools (e.g., King's College Criteria, MELD) to guide transplant decisions.
12. **Transplant Evaluation -** Engage transplant services early; initiate urgent evaluation and listing if criteria are met.

Step-wise management of Acute Liver Failure (ALF)

0. **Triage & immediate actions (first 10-30 minutes)**

- **Recognize ALF:** no prior cirrhosis + INR ≥1.5 + any encephalopathy (≤26 weeks from symptom onset).
- **ABCs:** high-flow O_2; two large-bore IVs; cardiac and pulse-ox monitoring; bedside glucose.
- **Stabilize:** treat hypoglycemia immediately (25-50 g IV dextrose; then D10 infusion). Start fluids (balanced crystalloids).
- **Labs (STAT, draw before fluids if possible):** CBC, CMP, AST/ALT, bilirubin, INR/PT, fibrinogen, ammonia (arterial if available), venous/arterial blood gas, lactate, pregnancy test, acetaminophen level, tox screen.
- **Cultures** (blood/urine ± sputum) if any infection concern.
- **Early calls: ICU bed;** transplant center notification if encephalopathy or rapid deterioration.

1. **First hour bundle**
   - **Airway:** intubate for West Haven **III-IV**, agitation, hypoxemia, or loss of airway reflexes. Target **SpO_2 ≥94%, $PaCO_2$ 35-40 mmHg.**
   - **Circulation:** aim **MAP ≥65 mmHg**. If hypotensive after 1-2 L crystalloid, start **norepinephrine**; add **vasopressin** if needed. Avoid overload.
   - **Start cause-directed therapy now (don't wait for results):**
     1. **N-acetylcysteine (NAC)** IV (acetaminophen or indeterminate ALF): 150 mg/kg over 1 h then 50 mg/kg over 4 h followed by 100 mg/kg over 16 h; continue 6.25 mg/kg/h if transaminases or INR still rising.
     2. **Suspected HBV reactivation:** start tenofovir DF 300 mg daily (or entecavir 0.5-1 mg daily) after drawing HBV DNA.
     3. **Autoimmune hepatitis flare:** if infection excluded and high suspicion, methylprednisolone 1-2 mg/kg/day.
   - **Stop hepatotoxins:** acetaminophen (if overdose), herbal remedies, halting non-essential meds; avoid NSAIDs.
2. **Neurologic protection (continuous from arrival)**
   - **Head-up 30°,** keep neck midline; avoid agitation and hypercapnia.
   - **Targets: Na 145-150 mmol/L, temp 36-37.5°C, glucose 140-200 mg/dL.**
   - **Cerebral edema treatment (if signs or ammonia >150-200 µmol/L):**
     - **Hypertonic saline 3%** bolus 150-300 mL (repeat to goal Na) or infusion; avoid rapid overcorrection.
     - **Mannitol 0.5-1 g/kg IV** if euvolemic and serum osmolality <320 mOsm/kg. Watch for rebound cerebral edema.
     - **Consider early CRRT** to lower ammonia and manage fluids.
   - **Seizure control:** levetiracetam preferred; avoid long-acting sedatives.
3. **Renal and metabolic management**
   - **Monitor** urine output hourly; correct hypovolemia.
   - **CRRT** when: severe hyperammonemia, progressive AKI, refractory acidosis, or fluid overload.
   - **Electrolytes:** replete K, Mg, P; correct Na slowly (≤8-10 mmol/L/24 h).

4. **Coagulopathy and bleeding/thrombosis**
   - **Do not "correct" INR** with FFP/platelets unless active bleeding or procedure planned. Give vitamin K 10 mg IV once if deficiency possible.
   - **VTE prophylaxis:** mechanical for all; pharmacologic if bleeding risk acceptable.
5. **Infection prevention and treatment**
   - **Low threshold for antibiotics** if fever, leukocytosis, hemodynamic instability, or new organ dysfunction; tailor to local flora.
   - **Daily reassessment;** replace/remove lines if suspected source.
6. **Etiology work-up (parallel with treatment)**
   - **Repeat acetaminophen level** at 4 h if timing uncertain.
   - **Viral panel:** HAV IgM, HBsAg ± HBV DNA, HCV RNA, HEV IgM (especially if pregnant/SE Asia).
   - **Autoimmune:** ANA, ASMA, IgG.
   - **Wilson (≤40 years or hemolysis):** ceruloplasmin, Coombs-negative hemolysis labs, 24-h urinary copper.
   - **Imaging:** RUQ **ultrasound with Doppler** (exclude obstruction; assess hepatic/portal flow, Budd-Chiari). Consider CT/MR if unclear.
7. **Ongoing ICU care (Day 0-1 and beyond)**
   - **Monitoring frequency:** neuro checks q1-2 h (early), vitals continuous, glucose hourly initially, labs (CMP, INR, ammonia, lactate) q6-8 h then daily as stable.
   - **Nutrition:** early enteral feeds if protected airway; protein restriction not routine.
   - **Stress ulcer prophylaxis** (ventilated/coagulopathy).
   - **Avoid lactulose** for HE in ALF (risk of bowel distension/aspiration; limited benefit).
   - **Document trends** (AST/ALT, INR, bilirubin, lactate, ammonia, creatinine) to judge trajectory.

8. **Prognostication & transplant pathway (do early, repeat often)**
   - **Apply King's College Criteria (KCC):**
     - **Acetaminophen:** pH <7.30 after resuscitation **OR** (INR >6.5 AND creatinine >3.4 mg/dL **AND** HE grades III-IV).
     - **Non-acetaminophen:** INR >6.5 OR any 3 of: age <10 or >40, unfavorable etiology (idiosyncratic DILI, non-A non-B), jaundice-to-HE >7 days, INR >3.5, bilirubin >17.5 mg/dL.
     - **Additional markers of danger:** lactate >3.5 mmol/L (4 h) or >3.0 (12 h) despite resuscitation; ammonia >150-200 µmol/L; rising creatinine; refractory shock.
     - **If criteria met or deterioration ongoing, urgent transplant evaluation/ listing;** continue NAC and full organ support.
9. **Special scenarios**
   - **Pregnancy (AFLP/HELLP or HEV):** coordinate with obstetrics; expedite delivery once stabilized.
   - **Amanita phalloides:** give silibinin (where available) and NAC; early transplant discussion.
   - **Wilsonian crisis:** rapid transplant referral; chelation rarely helps in ALF.
   - **Ischemic hepatitis:** prioritize hemodynamic correction; enzymes fall within 24-72 h once perfusion restored.
10. **Step-down & transition (recovery pathway)**
   - **Wean supports** as labs improve; stop vasopressors first, then reduce CRRT as tolerated.
   - **Complete NAC** once INR and transaminases clearly down-trending and acetaminophen cleared (or per protocol).
   - **Plan follow-up:** etiology-specific therapy (HBV antivirals continuation, AIH steroid taper), vaccination, counseling on medication safety and alcohol abstinence.

Note: Stabilize, treat the cause now, protect brain and kidneys, watch the numbers hourly, and call the transplant team early.

Figure 1. Clinical algorithm / flowchart for the Management of Acute Liver Failure (ALF), based on standard treatment guideline principles.

Pharmacological therapy When Exact Etiology is Known

Specific therapies are initiated only when the etiology is confirmed or strongly suspected. Supportive care should continue in parallel.

- **N-acetylcysteine (NAC):** First-line for acetaminophen ALF; also improves transplant-free survival in early non-acetaminophen ALF. Start immediately (ideally ≤8-10 h; still give later). Use IV (5% dextrose). Standard 21-h regimen; extend if injury persists. Cap weight at 100 kg for dosing. Manage nausea/anaphylactoid reactions by slowing infusion/antihistamines. Start before labs if overdose suspected.
- **Activated charcoal:** Give within 4 h of ingestion (paracetamol, amatoxin, many drugs) if airway protected.
- **Antivirals:**
  - **HBV:** tenofovir DF 300 mg daily (or entecavir).
  - **HSV/VZV:** acyclovir.
  - **CMV:** ganciclovir when indicated.
- **Corticosteroids:** For autoimmune hepatitis (after excluding infection). Avoid in uncontrolled sepsis or advanced coma.
- **Antibiotics/antifungals:** Use when infection suspected; tailor to cultures and local patterns.
- **Special scenarios:**
  - Wilson crisis, Budd-Chiari, AFLP/HELLP: urgent transplant/specialist pathway; consider therapeutic plasma exchange, IR procedures (e.g., TIPS for Budd-Chiari), or expedited delivery (AFLP/HELLP).

PHARMACOLOGICAL AGENTS IN ALF

Drug Class / Agent	Indication	Dose	Duration	Other Notes / Cautions
*N-acetylcysteine (NAC)	Paracetamol overdose, idiopathic ALF	150 mg/kg IV over 15 min then 50 mg/kg over 4 h followed by 100 mg/kg over 16 h	Until INR normalizes and mental status improves	Effective in non-paracetamol ALF as well
Acyclovir	Herpes simplex-related ALF	10 mg/kg IV every 8 h (renal adjust)	10-14 days	Start early, especially in pregnancy or immunocompromised
Corticosteroids	Autoimmune hepatitis	Methylprednisolone 1-2 mg/kg/day IV	Reassess at 5-7 days	Avoid in sepsis or Grade III/IV encephalopathy: taper if improving
Chelators (Penicillamine)	Wilson disease	250-500 mg PO daily (rarely used in ALF)	Bridge to transplant only	Not effective in ALF; High mortality; transplant preferred
Silibinin / Penicillin G	Amanita mushroom poisoning	Penicillin G: 300,000-1 million U/kg/day IV divided doses	3-5 days or until LFTs stabilize	Limited evidence; use NAC + supportive care; Silibinin preferred if available
Mannitol, Hypertonic saline	Cerebral edema	Mannitol: 0.5-1 g/kg IV bolus; 3% NaCl titrated	As needed	Monitor for volume overload and renal function
Broad-spectrum antibiotics	Suspected sepsis or infection	Piperacillin-Tazobactam 4.5 g IV every 6-8h OR Meropenem 1g IV every 8h	Based on clinical response	Empirical use; tailor once cultures available
Cefotaxime(alternative antibiotic)	Suspected infection/ Spontaneous Bacterial Peritonitis (SBP)	2 g IV every 8 h	5-7 days or as per infection	Renal dose adjustment needed; monitor for allergic reactions
Complications				
Proton pump inhibitors	Stress ulcer prophylaxis	Pantoprazole 40 mg IV daily	Until enteral feeding starts	Use in intubated patients or those on steroids
Low-molecular-weight heparin	DVT prophylaxis	Enoxaparin 40 mg SC daily (if safe coagulation profile)	Until ambulation/ discharge	Avoid if platelets <50,000 or INR >2.5
Insulin, electrolytes	Metabolic stabilization	Titrate insulin IV infusion to glucose 140-180 mg/dL	Continuous	Correct hypo/ hypernatremia, hypokalemia
Vitamin K	Coagulopathy (if vitamin K deficiency)	10 mg IV once	Single dose; repeat if INR improves	No benefit in if the liver has lost its ability to produce clotting factors (i.e., synthetic liver failure)

Renal replacement therapy	AKI, hyperammonemia	CVVH (Continuous Veno-Venous Hemofiltration) or IHD (Intermittent Hemodialysis prescribed and adjusted based on ICU protocol and patient stability	Until renal recovery/ transplant	CVVH preferred in hemodynamically unstable patients; effective in lowering ammonia and managing acid-base balance. Requires central venous access and close monitoring of electrolytes and fluid status
Plasma exchange	A promising strategy for treating patients with ALF, it is not widely available	high-volume plasma exchange		

MANAGEMENT OF COMPLICATIONS IN ALF

Preventing progression to multi-organ dysfunction is central to the management of Acute Liver Failure. Early identification and timely intervention for complications can improve survival and avoid irreversible deterioration.

Renal failure

- **Causes:** hypovolemia, acute tubular necrosis, hepatorenal syndrome.
- **If hypotensive:** start norepinephrine (first-line) or dopamine if bradycardic/selected cases.
- **Prefer CRRT over intermittent hemodialysis in unstable patients;** use as a bridge to transplant.
- **Track urine output hourly;** avoid nephrotoxins; correct volume and electrolytes.

Sepsis/infections

- **Common sources:** aspiration pneumonia, catheter-related, spontaneous bacteremia.
- **Start empiric broad-spectrum antibiotics with fever, hypotension, new organ dysfunction, or leukocytosis;** de-escalate to cultures.
- Obtain surveillance cultures (blood, urine, sputum) and reassess daily; remove/ replace suspect lines.

Metabolic derangements

- **Hypoglycemia:** run 10-20% dextrose infusion with hourly glucose checks early.
- **Hypophosphatemia:** replete promptly (supports ATP and diaphragmatic function).
- **Acid-base:** respiratory alkalosis is common; pH <7.30 (esp. acetaminophen ALF) = poor prognosis; urgent transplant evaluation required.
- **Hypoxemia:** from aspiration/ARDS/pulmonary hemorrhage-use lung-protective ventilation.
- **Airway:** intubate for HE grade ≥3 or loss of airway reflexes.
- **Seizures:** treat with levetiracetam or phenytoin; benzodiazepines only if needed and airway protected.

Cerebral edema / intracranial hypertension

- High risk with arterial ammonia >200 µmol/L; watch for abnormal pupils, rigidity, decerebrate posturing.
- Targets (if ICP monitoring available): ICP <25 mmHg, CPP >50 mmHg.
- Measures: head-up 30°, minimize stimulation, sedate and intubate for advanced HE, vasopressors to maintain CPP, CRRT for ammonia, hypertonic saline (keep Na 145-155 mEq/L), mannitol IV if euvolemic, brief hyperventilation for acute spikes.

Hepatic encephalopathy (HE)

- Defining feature of ALF; rapid progression possible.
- For grade ≥3, get non-contrast head CT to exclude bleed/marked edema and secure airway.
- Hunt and treat precipitants: infection, GI bleeding, electrolyte disorders, hypoglycemia.

Coagulopathy

- Elevated PT/INR; major bleeding is uncommon.
- Do not correct INR routinely. Give plasma/platelets/cryoprecipitate only for active bleeding or procedures.
- Vitamin K IV if deficiency or cholestasis suspected.
- Recombinant factor VIIa: reserve for rescue; thrombotic risk.

Monitoring & Safety Considerations in ALF

- **Renal/hepatic dosing:** Adjust all renally cleared and hepatically metabolized drugs (antivirals, antibiotics, sedatives, anticoagulants). Re-calculate doses daily as creatinine, urine output, and liver tests change.
- **Avoid hepatotoxins:** Stop non-essential drugs (NSAIDs, valproate, isoniazid/rifampicin combos, herbal supplements). Prefer IV routes if vomiting/ileus.
- **Airway-safe sedation:** Avoid long-acting benzodiazepines and opioids; use short-acting agents (e.g., propofol in ICU) with airway protected.
- **N-acetylcysteine (NAC):** Start early; continue or extend if INR/ALT remain high. Watch for anaphylactoid reactions during loading - give slow infusion and antihistamines if needed.
- **Antivirals:**
  - **Tenofovir/entecavir (HBV):** Renal dose adjustments; monitor creatinine and phosphate.
  - **Acyclovir/ganciclovir:** Renal dosing mandatory; watch for neurotoxicity (acyclovir) and cytopenias (ganciclovir).
- **Antibiotics:** Choose broad coverage when infection suspected; avoid nephrotoxins (aminoglycosides) where possible. If used, monitor drug levels (e.g., vancomycin troughs), creatinine, and auditory status.
- **Drug levels/therapeutic monitoring:** Check acetaminophen concentration until undetectable; follow vancomycin (AUC/trough), aminoglycosides (peaks/troughs), and antifungal levels when applicable.
- **Interaction checks:** Screen for CYP and QT-prolonging interactions (macrolides, fluoroquinolones, azoles, methadone, antipsychotics). Reconcile meds at every shift; limit polypharmacy.
- **Coagulation & procedures:** Do not correct INR solely to normalize labs; give blood products only for bleeding or procedures. Consider DVT prophylaxis if bleeding risk acceptable.
- **Electrolytes & glucose:** Hourly glucose early (continuous dextrose as needed). Replace K, Mg, and phosphate promptly (supports diaphragm/ATP). Maintain Na targets if using hypertonic therapy.
- **Renal support & dosing on CRRT:** When on CRRT, recalculate & adjust doses (many drugs clear faster). Confirm with pharmacy dosing guides.

- **Ammonia & neuro safety:** Track ammonia trends; avoid lactulose routinely in ALF (aspiration/ileus risk). Treat seizures with levetiracetam or phenytoin; avoid oversedation.
- **Documentation & handoffs:** Chart indication, dose, route, renal/hepatic adjustments, stop dates, and monitoring plan for every drug; use checklists at each handoff.

NON PHARMACOLOGICAL INTERVENTIONS IN ALF

Non-pharmacological strategies are essential in the supportive care of patients with acute liver failure and can significantly influence outcomes.

- Intensive monitoring in a critical care setting allows early detection of deterioration and prompt intervention.
- Nutritional support should be initiated early, preferably via the enteral route, aiming for 25-30 kcal/kg/day with adequate protein, unless encephalopathy worsens.
- Neuroprotective measures are crucial to prevent or manage cerebral edema and include head elevation, minimal stimulation, sedation protocols, and, when indicated, intracranial pressure (ICP) monitoring in high-risk patients.
- Airway protection is vital in patients with grade ≥3 encephalopathy, often requiring mechanical ventilation.
- Fluid balance should be carefully maintained to prevent volume overload.
- Renal replacement therapy (RRT) should be used for refractory acute kidney injury (AKI), hyperammonemia, or fluid overload.
- Temperature control is also important; patients should be kept normothermic to reduce metabolic stress.
- Infection control through strict aseptic techniques is critical, given the high risk of sepsis in ALF.
- Psychosocial support for patients and families, especially in cases requiring transplant planning, and involvement of a multidisciplinary team, including hepatology, critical care, infectious diseases, and transplant coordination, holistic care.

- Early referral to a liver transplant center is essential for eligible patients, allowing timely evaluation and potential listing before irreversible decompensation occurs.

ASSESSMENT OF RESPONSE IN ALF

Domain	What to track	Frequency	Desired trend / target	Act if worsening	Escalation trigger
Neurologic (HE)	West Haven grade, pupils, GCS	q1-2 h (ICU)	Improving mentation; stable pupils; no seizures	Optimize sedation/airway; correct glucose/ electrolytes; manage ammonia (CRRT)	Progression to HE III-IV, seizures, signs of raised ICP
Hemodynamics	MAP, HR, lactate, temperature	Continuous + lactate q6-12 h	MAP ≥65 mmHg; falling lactate	Fluids, norepinephrine ± vasopressin; source control	Persistent shock, rising lactate despite resuscitation
Coagulation	INR, fibrinogen, platelets	Daily (q12 h if unstable)	INR declining, fibrinogen >150 mg/dL	Vitamin K if deficiency; products only for bleeding/ procedure	INR ≥6.5 or rapid rise
Liver injury	AST/ALT, bilirubin	Daily	Down-trending AST/ALT; bilirubin stabilizing/falling	Recheck etiology; continue/extend NAC	Worsening labs despite therapy
Ammonia	Arterial ammonia	Daily (q6-12 h if HE)	<100 µmol/L or falling	Intensify CRRT; hypertonic saline target Na 145-150	>150-200 µmol/L or rising with HE
Renal	Creatinine, urine output, balance	q6-12 h	UO ≥0.5 mL/kg/h; stable/↓ creatinine	Optimize volume; start CRRT if AKI/ overload	Progressive AKI, anuria, refractory acidosis
Metabolic	Glucose, Na/K/ Mg/Phos, ABG	Glucose hourly early; electrolytes q6-12 h	Glucose 140-200 mg/dL; electrolytes in range; pH normalizing	D10-20 infusion; replace deficits; adjust ventilation	pH <7.30 (esp. acetaminophen), refractory derangements
Infection	Cultures (blood/ urine/sputum), WBC, procalcitonin (adjunct)	Cultures on admit and with change; daily review	Afebrile, cultures negative or clearing	Start/adjust antibiotics; remove suspect lines	Sepsis, fungemia, persistent bacteremia
Imaging	RUQ US/Doppler; CT brain (HE ≥3 or focal signs)	As indicated	No obstruction/ bleed/ICP lesion	ERCP, IR, neuro-surveillance per findings	New bleed, obstruction, cerebral edema

Issues before step-up/step-down in treatment

Before transitioning, either escalating (step-up) or de-escalating (step-down), several clinical and contextual factors as below must be thoroughly evaluated:

- Hemodynamic instability (pressors vs. fluid)
- Rising intracranial pressure (Mannitol vs. hypothermia)
- Persistent coagulopathy despite vitamin K
- Worsening renal function (initiate RRT)
- Presence of ongoing or unresolved complications (e.g. sepsis, encephalopathy). Active infection (escalate antimicrobials)
- Trends in biochemical markers (e.g. liver enzymes, INR, renal function)

Step-up and re-check transplant criteria

Any deterioration in HE, INR, lactate, ammonia, pH, creatinine, or hemodynamics

Step-down

Sustained improvement across these domains with stable airway, off pressors, and controlled infection, step down carefully, with explicit monitoring and stop dates.

REFERRAL FOR SPECIALIST CONSULTATION& TRANSFER

Trigger for referral	Time frame	Immediate actions at referring site	Teleconsultation goals	Transfer logistics
King's College Criteria met (APAP or non-APAP)	Immediate	Activate transplant pathway; continue NAC and full organ support	Confirm candidacy; agree on escalation steps	Arrange priority transport; notify receiving ICU
High or rising MELD/ MELD-Na (or MELD 3.0)	Immediate if rising despite care	Intensify monitoring; correct reversible factors	Risk stratify; decide on listing urgency	Pre-alert transplant coordination team
No clinical improvement within 24-72 h despite optimal care	Within 72 h	Review bundle: airway, MAP, CRRT, infection control	Reassess prognosis; determine next steps	Book transfer window; share interval labs
Worsening HE (≥III), ammonia >150-200 µmol/L, or ICP concern	Immediate	Intubate; hypertonic therapy; consider CRRT	Brain protection plan; eligibility with neuro status	Transport with ventilator and hypertonic protocol

Refractory shock or rising lactate	Immediate	Vasopressors; source control; lactate-guided resuscitation	Decide on futility vs transplant	Critical care transport with vasopressors running
Rapidly worsening INR (≥6.5) or bilirubin ≥17.5 mg/dL	Immediate	Vitamin K if deficiency; avoid prophylactic FFP	Prognosis confirmation; listing discussion	Ensure access/bloods; avoid product loading pre-transfer
Special etiologies (Amanita, Wilson crisis, HBV flare, AFLP/HELLP, Budd-Chiari)	Immediate	Start specific therapy; involve OB/IR as needed	Define bridge therapy vs emergent listing	Coordinate specialty teams at receiving center

Note: If criteria are met or the patient fails to improve within 72 hours, call and transfer early; don't wait for further deterioration.

What to include in the first teleconsult

Packet element	Details to send
Timeline	Onset of jaundice, time to HE, therapies given (NAC start/stop), fluids/pressors
Vitals/organ support	Airway status, ventilation settings, MAP/pressors, CRRT settings/ultrafiltration
Key labs (latest + trends)	INR/PT, bilirubin, AST/ALT, creatinine/urine output, ammonia, lactate, ABG/pH
Etiology workup	APAP levels (serial), HAV/HBV/HCV/HEV, ANA/ASMA/IgG, ceruloplasmin/ hemolysis, tox screen
Imaging	RUQ US/Doppler, CT brain if HE ≥III
Contraindications/risks	Active infections, bleeding, pregnancy status, comorbidities
Contacts/logistics	Referring to ICU lead, transport ETA, bed request number

Transport readiness checklist

1. Airway secured (HE ≥III) and ventilator-compatible transport settings
2. Hemodynamic support running (pressors on pumps; spare syringes)
3. Hypertonic therapy plan (Na target 145-150; mannitol PRN)
4. CRRT: continue if feasible or pause safely; share last filter times and settings
5. Medication list + doses (NAC, antivirals, antibiotics, sedation) with stop/start times
6. Printed/electronic trend graphs for INR, ammonia, lactate, creatinine, AST/ALT
7. Consent and documents for transplant evaluation started.

COMPLICATIONS: ALF

Complications in ALF aren't just side effects-they can be rapidly fatal and often determine the clinical outcome. Because the liver plays a central role in metabolism, coagulation, detoxification, and immune regulation, its failure disrupts multiple systems.

Complication	Pathophysiology / Key clues	Monitor	Initial management / Key actions
Cerebral edema & intracranial hypertension	Hyperammonemia due to astrocyte swelling; highest risk in HE III-IV, ammonia >150-200 µmol/L	Neuro checks, pupils, ammonia, Na; consider ICP monitor (selected)	Head-up 30°, avoid hypercapnia; target Na 145-150 (hypertonic saline); mannitol 0.5-1 g/kg IV if euvolemic; early CRRT for ammonia; treat seizures (levetiracetam); avoid routine lactulose
Hepatic encephalopathy progression	Rapid shift confusion progressing to coma	Serial mental status, airway protection threshold	Minimize sedatives; intubate HE III-IV; correct hypoglycemia/ electrolytes; treat infection/ precipitant
Circulatory failure (vasoplegia/ shock)	Systemic vasodilation ± myocardial depression; high lactate	MAP, lactate, urine output	Balanced crystalloids; norepinephrine first-line, add vasopressin if needed; source control of sepsis
Acute kidney injury (AKI)	Prerenal/ATN; cytokine-mediated renal vasoconstriction	Creatinine, urine output	Volume optimization; vasopressors for MAP ≥65; avoid nephrotoxins; early CRRT (ammonia control/ hemodynamics)
Coagulopathy (bleeding &thrombosis)	Rebalanced hemostasis: bleeding risk and VTE risk coexist	INR, fibrinogen, platelets; clinical bleeding	Vitamin K if deficiency; avoid prophylactic FFP/platelets unless bleeding/procedure; mechanical VTE prophylaxis ± pharmacologic if safe
Infection & sepsis	Immune paresis leading to bacterial/ fungal infection	Vitals, cultures, procalcitonin as adjunct	Early, targeted antibiotics/ antifungals when suspected; remove/replace lines; source control
Respiratory failure / ARDS / aspiration	Encephalopathy, sepsis, volume overload	SpO_2/ABG, CXR	Early intubation if HE advanced; lung-protective ventilation; conservative fluids after resuscitation
Metabolic: hypoglycemia	Loss of gluconeogenesis	Hourly glucose initially	Continuous dextrose infusion; avoid wide swings
Metabolic: lactic acidosis	Poor clearance/shock	Lactate trends	Optimize perfusion; CRRT if severe
Electrolyte disorders	Hypo/HyperNa, K, P, Mg	Electrolyte panel	Correct gradually (Na), replace deficits; watch QT/arrhythmias
GI bleeding / stress ulcers	Coagulopathy, critical illness	Hemoglobin, stool/ NG output	PPI prophylaxis (ventilated/ coagulopathic); urgent endoscopy if feasible
Relative adrenal insufficiency	Refractory shock despite fluids/ pressors	Random cortisol (if available)	Consider stress-dose hydrocortisone after covering infection
Multiorgan failure / poor prognosis	Rising SOFA/CLIF-OF; worsening HE, lactate, ammonia	Daily organ scores; trend labs	Immediate transplant-center discussion; continue NAC where indicated; escalate organ support

PROGNOSIS AND SURVIVAL WITHOUT LIVER TRANSPLANTATION

Survival rates in ALF are highly dependent on the underlying etiology. According to data from a large registry-based study, overall transplant-free survival across all patient groups is approximately 50%.

- Etiology drives prognosis. Transplant-free survival varies widely by cause.
- Overall transplant-free survival ~50%. Registry data show about half survives without transplant.
- Outcomes have improved. Survival has risen from ~20% to >60% over recent decades with modern ICU care and timely transplantation.
- Early recognition is pivotal. Look for INR elevation (synthetic failure), marked aminotransferase rise, hyperammonemia, and neurologic change (confusion progressing to coma).
- Act fast. Start cause-directed therapy (e.g., NAC), protect airway in advanced encephalopathy, and call the transplant center early if poor-prognosis criteria are met.
- Continuous reassessment. Trending INR, ammonia, lactate, creatinine, mental status guides escalation and transplant decisions.

PREVENTION AND HEALTH PROMOTION

- Vaccination & screening: Sustain HBV birth-dose within 24 h, full HBV schedule, HCW vaccination; targeted HBV/HCV testing (antenatal, dialysis, high-risk groups) with linkage to care.
- Water, sanitation, food safety: Strengthen safe water and sewage on islands; HAV/HEV prevention via hygiene, safe seafood, and rapid evaluation of jaundice in pregnancy.
- Medication safety: Public messaging on safe paracetamol dosing; avoid unknown supplements/herbals; island hospitals keep IV NAC and an ALF protocol ready.
- NCD & MASLD control: Integrate weight management, diabetes/lipid control, and liver-smart diet/activity advice into primary care and NCD clinics.
- Alcohol & toxins: Risk communication in tourism/expat settings; workplace chemical safety; discourage foraged/mystery mushrooms and counterfeit remedies.

- Infection control: Safe transfusion, sharps safety, early sepsis treatment; routine HBV vaccination and post-exposure prophylaxis for health workers.
- Early recognition & referral: Standard ALF bundle (INR, AST/ALT, ammonia, mental status) at atoll hospitals; tele-hepatology links to Malé/regional centers; pre-agreed air/sea transfer pathways.
- Systems enablers: Ensure stocks (NAC, antivirals), staff training and drills, simple national registry for acute jaundice/ALF, and community outreach: "Jaundice + confusion = emergency."

PATIENT EDUCATION

Acute liver failure is an ICU emergency. Decisions are time-sensitive, and transplant may be needed. Because patients can be confused or unconscious, most guidance is for caregivers. Patient education focuses on helping families understand the seriousness of the illness, the need for close monitoring, and potential outcomes, including liver transplant. Clear communication, timely decisions, and adherence to medical guidance can significantly improve outcomes in ALF.

What to expect

- Continuous monitoring, possible ventilator, dialysis (CRRT), and medicines to control brain swelling, infection, and bleeding risks.
- The team will reassess for transplant daily if recovery is uncertain.
- After discharge (if not transplanted)
- No alcohol. Avoid unapproved drugs/supplements.
- Attend all follow-ups; carry a summary of hospitalization and lab trends.
- Return urgently for confusion, fever, bleeding, severe vomiting, or worsening jaundice.

Instructions to the patients and caregivers

Do	Don't
• Follow hospital instructions exactly; ask if anything is unclear.	• Don't give any medicine (OTC, herbal, "home" remedies) unless approved by the team.
• Stay at the bedside or reachable; designate one decision-maker.	• Don't allow alcohol or sedatives not prescribed in ICU.
• Bring a full medication list (including herbals/ supplements) and allergies.	• Don't remove lines, devices, or feeds, and don't leave against medical advice.
• Authorize early referrals/teleconsultation with transplant centers when advised.	• Don't delay transfer if the team recommends a higher-level or transplant center.
• Report changes fast: new confusion, severe drowsiness, fever, bleeding, black stools, shortness of breath, reduced urine, worsening jaundice.	• Don't hide ingestion history (paracetamol, herbals, toxins); accuracy saves time.
• Agree to frequent tests and monitoring (bloods, scans, cultures).	
• Plan follow-up with a liver specialist before discharge; know warning signs after discharge.	
• If confusion or excessive sleepiness appears with jaundice- treat it as an emergency and inform the team immediately.	

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