Approach to a child with acute elevation of liver enzymes

Rajeev Khanna

www.ispghan.org

Acute hepatitis is a clinical syndrome characterized by acute onset of liver dysfunction (usually over a period 4 weeks) characterized by elevation of transaminases with variable synthetic dysfunction. Acute hepatitis should be suspected when a child presents with a combination of features comprised of jaundice, nausea, vomitings and pain over right upper quadrant. In a large majority of children with acute febrile illness, the syndrome comes into light just incidentally on routine blood tests. **Table 1** gives various laboratory pointers and **Figure 1** provides algorithmic approach to children with acute hepatitis.

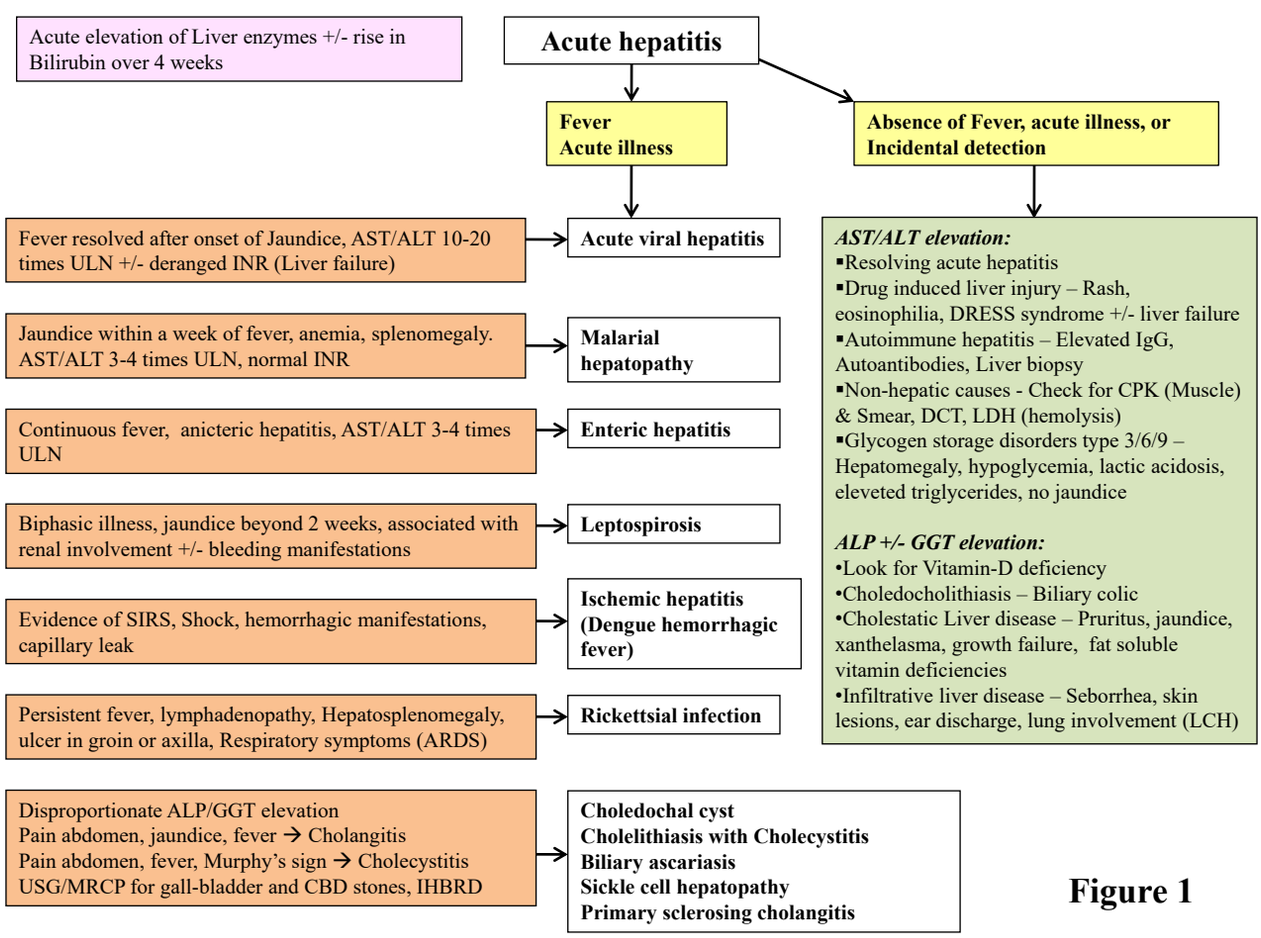

Figure 1

Figure 1. Algorithmic approach to a child with acute hepatitis with and without fever. Abbreviations: ALP = Alkaline phosphatase; ALT = Alanine transaminase; ARDS = Acute respiratory distress syndrome; AST = Aspartate transaminase; CBD = Common bile duct; CPK = Creatine phosphokinase; DCT = Direct Coomb's test; DRESS = Drug rash eosinophilia systemic symptoms; IgG = Immunoglobulin G; IHBRD = Intrahepatic biliary radical dilatation; GGT = Gammaglutamyl transpeptidase; LCH = Langerhans cell histiocytosis; LDH = Lactate dehydrogenase; MRCP = magnetic resonance cholangiopancreaticography; SIRS = systemic inflammatory response syndrome; ULN = Upper limit of normal; USG = Ultrasonography.

Additional Professor, Department of Pediatric Hepatology, Institute of Liver and Biliary Sciences, New Delhi.

Table 1: Clinical and laboratory pointers to diagnosis in a child with acute hepatitis

Clinical pointers	**Diagnosis**
Fever, sore throat, cervical lymphadenopathy, splenomegaly (Infectious mononucleosis)	EBV CMV
Fever, exanthematous rash (vesicular) Fulminant hepatitis in immunocompromised states	VZV
Fever, exanthematous rash (vesicular) Fulminant hepatitis in neonates or immunodeficient children	HSV
Fever, upper respiratory symptoms, cervical lymphadenopathy, followed by transient (3-day) exanthematous rash (maculopapular) over trunk (exanthema subitum), Nagayama spots	HHV-6
Fever, facial rash (slapped cheek appearance), Polyarthritis, aplastic crisis in chronic hemolytic states (erythema infectiosum)	Parvovirus B19
Fever, rash, itching ± systemic features, eosinophilia	Drug induced liver injury
Pallor with cola-coloured urine	Malaria, G-6-P-D deficiency Wilson's disease
Acute pain right upper quadrant, fever, Positive Murphy's sign, High TLC	Acute Cholecystitis
Intermittent biliary pain with mild elevation of bilirubin and ALP/GGT	Choledocholithiasis
Pain right upper quadrant, fever, jaundice (Charcot's triad), High TLC, band forms, positive culture	Cholangitis#
ICU setting with severe sepsis, shock or haemorrhage	Ischemic hepatitis
Pain abdomen, tender hepatomegaly, prominent abdominal and back veins, pedal edema, absent hepatojugular reflex	Acute Budd-chiari syndrome
Pain abdomen, tender hepatomegaly, present hepatojugular reflex, raised jugular venous pressure	Congestive heart failure
Laboratory pointers	
Marked AST & ALT elevation (in 1000s, >20 ULN)	Viral hepatitis, Ischemic hepatitis Drug induced (Paracetemol) Autoimmune hepatitis Acute Budd-Chiari syndrome
Moderate AST & ALT elevation (in 100s, 3-20 ULN)	Viral hepatitis Wilson disease Autoimmune hepatitis Drug induced hepatitis Acute passage of gall stone$
Mildly elevated AST & ALT (<3 ULN)	Malaria, Typhoid fever, Sepsis, Leptospirosis
Biphasic illness, thrombocytopenia, rhabdomyolysis, renal failure, haemorrhagic manifestations, elevated creatine kinase	Leptospirosis
AST & ALT in 1000s and AST/ALT ratio > 1	Ischemic hepatitis Dengue fever
AST & ALT in 100s and AST/ALT ratio > 1, ALP (IU/L) / Bilirubin (mg/dL) ratio < 2 Coomb's negative hemolysis, Kayser Fleischer ring in Cornea	Wilson's disease
Coomb's positive hemolysis, Reversal of Albumin:Globulin ratio with elevated IgG Positive autoantibodies (anti-nuclear, anti-smooth muscle, anti-liver kidney microsomal)	Autoimmune hepatitis
ALT/LDH ratio	<4 → Typhoid fever >5 → Viral hepatitis
Fever with Thrombocytopenia (± Leukopenia)	Dengue fever Enteric fever Complicated malaria Gram-negative sepsis HLH
Fever, splenomegaly, hypertriglyceridemia (>265 mg/dL), hypofibrinogenemia (<1.5 g/L), hyperferritinemia (>500 microgm/L), hemophagocytosis in bone marrow, spleen or lymph nodes	HLH

ALP = Alkaline phosphatase; ALT = Alanine transaminase; AST = Aspartate transaminase; CMV = Cytomegalovirus; EBV = Epstein-Barr virus; HHV = Human herpes virus; HSV = Human herpes virus; G-6-P-D = Glucose-6-Phosphatase dehydrogenase; HLH = Haemophagocyticlymphohistiocytosis; ICU = Intensive care unit; LDH = Lactate dehydrogenase; TLC = Total leukocyte count; ULN = Upper limit of normal; VZV = Varicella-zoster virus. #Cholangitis may happen in the setting of Choledocholithiasis, Biliary atresia, Primary sclerosing cholangitis, Biliary ascariasis. Typical triad is seen in 75% (in adults); hypotension and altered mentation (Reynold pentad) is seen in 15% (in adults). $Acute passage of gall stone through the ampulla is associated with biliary pain and modest elevation of AST/ALT and ALP (upto 5-10 times ULN) +/- elevation of serum amylase.

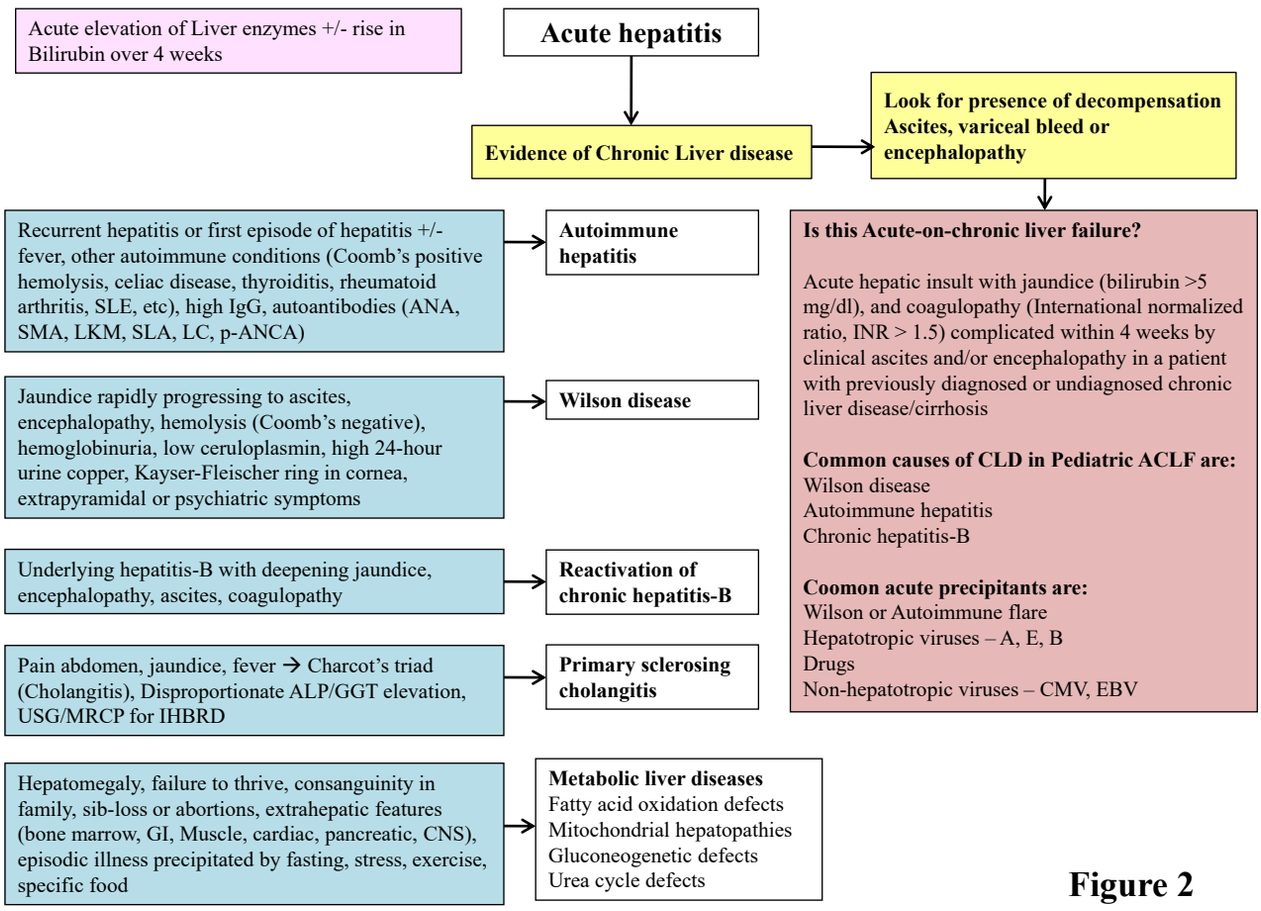

Figure 2

Figure 2. Algorithmic approach to a child with acute hepatitis as first manifestation of underlying chronic liver disease. Abbreviations: ACLF = Acute-on-chronic liver failure; ALP = Alkaline phosphatase; ALT = Alanine transaminase; ANA = Anti-nuclear antibody; AST = Aspartate transaminase; CLD = Chronic liver disease; CMV = Cytomegalovirus; CNS = Central nervous system; EBV = Epstein Barr virus; GI = Gastrointestinal; IgG = Immunoglobulin G; IHBRD = Intrahepatic biliary radical dilatation; GGT = Gamma-glutamyl transpeptidase; LC = Liver cytosolic antibodies; LCH = Langerhans cell histiocytosis; LDH = Lactate dehydrogenase; LKM = Anti-liver kidney microsomal antibody; MRCP = magnetic resonance cholangiopancreaticography; p-ANCA = perinuclear anti-neutrophilic cytoplasmic antibodies; SIRS = systemic inflammatory response syndrome; SLA = Antibodies to soluble liver antigen; SLE = Systemic lupus erythematosus; SMA = Anti-smooth muscle antibody; ULN = Upper limit of normal; USG = Ultrasonography.

Firstly, predominant elevation of transaminases (Aspartate transaminase, AST and Alanine transaminase, ALT, >40 IU/L) should be differentiated from predominant elevation of cholestatic enzymes (alkaline phosphatase, ALP, >3 times ULN for age and gamma-glutamyl transpeptidase, GGT, >2 times ULN) to separate hepatic parenchymal causes from cholestatic or biliary causes. Acute hepatitis when accompanied by coagulopathy or encephalopathy is termed as ***acute liver failure***. For pediatric age-group (0-18 years) we should follow the definition given by Pediatric acute liver failure study group (PALFSG) i.e. biochemical evidence of acute liver injury with no known evidence of chronic liver disease, and hepatic-based coagulopathy defined as a prothrombin time (PT) > 15 seconds or international normalized ratio (INR) > 1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy (HE), or a PT > 20 seconds or INR > 2.0 regardless of the presence or absence of clinical HE. In all cases of acute hepatitis, ***stigmata of chronic liver disease*** (CLD) should be looked for as these may be a first manifestation of underlying CLD i.e. growth failure, palmar erythema, spider nevi, facial telangiectasia, clubbing, pedal edema, features of fat soluble vitamin deficiencies, xanthelasma, scratch marks (for cholestatic pruritus), hyperpigmentation. **Figure 2** gives pointers to an underlying CLD with first presentation as acute hepatitis.

FURTHER READING:

1. Poddar U, Thapa BR, Prasad A, Singh K.Changing spectrum of sporadic acute viral hepatitis in Indian children. *J Trop Pediatr*. 2002 Aug;48 (4):210-3.
2. Squires RH Jr, Shneider BL, Bucuvalas J, Alonso E, Sokol RJ, Narkewicz MR, et al. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. *J Pediatr*. 2006 May;148 (5):652-658.
3. Alam S, Lal BB, Sood V, Rawat D. Pediatric Acute-on-Chronic Liver Failure in a Specialized Liver Unit: Prevalence, Profile, Outcome, and Predictive Factors. *J Pediatr Gastroenterol Nutr*. 2016 Oct;63 (4):400-5.
4. Alam S, Khanna R, Sood V, Lal BB, Rawat D. Profile and outcome of first 109 cases of paediatric acute liver failure at a specialized paediatric liver unit in India. *Liver Int*. 2017 Oct;37 (10):1508-1514.
5. Cooper EC, Ratnam I, Mohebbi M, Ledder K. Laboratory features of common causes of fever in returned travelers. J Travel Medicine 2014;21 (4):235-239.

6. Kothari VM, Karnad DR, Bichile LS. Tropical infections in the ICU. *JAPI* 2006;54:291-298.
7. Anand AC, Garg HK. Approach to clinical syndrome of jaundice and encephalopathy in tropics. J Clin Exp Hepatol 2015;5:S116-S130.
8. Walker NF, Nadzim B, Whitty CJM. Malaria. *Medicine* 2014;42 (2):100-106.
9. Saravu K, Rishikesh K, Kamath A. Determinants of mortality, intensity care requirement and prolonged hospitalization in malaria – a tertiary care hospital based cohort study from South-Western India. *Malaria Journal* 2014;13:370.
10. Samanta J, Sharma V. Dengue and its effects on liver. *World J Clin Cases* 2015;3 (2):125-131.
11. Coursin DB, Updike SJ, Maki DG. Massive rhabdomyolysis and multiple organ dysfunction syndrome caused by Leptospirosis. *Intensive Care Med* 2000;26:808-812.
12. Pugliese A, Beltramo T, Torre D. Reye's and Reye's like syndromes. *Cell Biochem Funct* 2008;26:741-746.
13. Socha P, Janczyk W, Dhawan A, Baumann U, D'Antiga L, Tanner S, et al. Wilson's Disease in Children: A Position Paper by the Hepatology Committee of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2018 Feb;66 (2):334-344.
14. Mieli-Vergani G, Vergani D, Baumann U, Czubkowski P, Debray D, Dezsofi A, et al. Diagnosis and Management of Pediatric Autoimmune Liver Disease: ESPGHAN Hepatology Committee Position Statement. *J Pediatr Gastroenterol Nutr.* 2018 Feb;66 (2):345-360.
15. Brisse E, Wouters CH, Matthys P. Hemophagocytic lymphohistiocytosis (HLH): A heterogeneous spectrum of cytokine-driven immune disorders. *Cytokine Growth Factor Rev*. 2015 Jun;26 (3):263-80.