Acute Liver Dysfunction Criteria in Critically Ill Children: The PODIUM Consensus Conference

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CONTEXT: Develop evidence-based criteria for individual organ dysfunction.

OBJECTIVES: Evaluate current evidence and develop contemporary consensus criteria for acute liver dysfunction with associated outcomes in critically ill children.

DATA SOURCES: Electronic searches of PubMed and Embase conducted from January 1992 to January 2020, used medical subject heading terms and text words to characterize acute liver dysfunction and outcomes.

STUDY SELECTION: Studies evaluating critically ill children with acute liver dysfunction, assessed screening tools, and outcomes were included. Studies evaluating adults, infants ≤36 weeks gestational age, or animals or were reviews/commentaries, case series with sample size ≤10, or non-English language studies were excluded.

DATA EXTRACTION: Data were abstracted from each eligible study into a data extraction form along with risk of bias assessment by a task force member.

RESULTS: The systematic review supports criteria for acute liver dysfunction, in the absence of known chronic liver disease, as having onset of symptoms <8 weeks, combined with biochemical evidence of acute liver injury, and liver-based coagulopathy, with hepatic encephalopathy required for an international normalized ratio between 1.5 and 2.0.

LIMITATIONS: Unable to assess acute-on-chronic liver dysfunction, subjective nature of hepatic encephalopathy, relevant articles missed by reviewers.

CONCLUSIONS: Proposed criteria identify an infant, child, or adolescent who has reached a clinical threshold where any of the 3 outcomes (alive with native liver, death, or liver transplant) are possible and should prompt an urgent liaison with a recognized pediatric liver transplant center if liver failure is the principal driver of multiple organ dysfunction.
Acute liver failure (ALF) is a complex and dynamic clinical syndrome. In 1970, Trey and Davidson\(^1\) codified acute liver failure in adults as the presence of hepatic coma within 8 weeks of jaundice with the presumption of normal liver function before onset of illness based on their findings in the fulminant hepatic failure surveillance study in Boston, Massachusetts. Most cases in this early study were due to presumed viral hepatitis, blood product transfusion, and halothane toxicity. In 1989, Kings College Hospital criteria (KCHC) were established to determine early prognostic factors in adults with either acetaminophen- or non-acetaminophen-induced ALF.\(^2\) Data elements included in the KCHC were a specific time interval between onset of jaundice and encephalopathy, patient age, total bilirubin level, international normalization ratio (INR), diagnosis, arterial pH, and creatinine. Subsequently, there have been over 40 “definitions” of acute liver failure, making comparisons between studies difficult.\(^3\) Significant differences between adults and children with ALF have been identified including etiology, development of encephalopathy, underlying pathophysiology, and outcomes. As pediatric acute liver failure (PALF) is rare, a collaborative effort was needed to advance our understanding of PALF.

The National Institutes of Health funded the multicenter, multinational Pediatric Acute Liver Failure Study Group in 1999 to tackle many unmet needs associated with PALF. Entry criteria for the PALF study, which serve as the basis for our proposed Pediatric Organ Dysfunction Information Update Mandate (PODIUM) criteria, were established by consensus from principal investigators at 24 participating pediatric liver transplant sites in the United States, Canada, and England.\(^4\) To enhance universal acceptance and rapid recognition of PALF, clinical and laboratory elements that comprised the entry criteria were selected that could be used in health care facilities worldwide. Study criteria were established to uniformly identify a patient cohort at potential risk for a poor outcome and were not intended to predict an outcome. The PALF study entry criteria have proven capable of capturing individuals at risk for death or in need of a liver transplant.\(^5,6\)

An important caveat is that these criteria were not developed for patients with known chronic liver disease who develop acute decompensation in liver function (a.k.a. acute-on-chronic liver failure). Published consensus recommendations in diagnosis and management of acute-on-chronic liver failure (ACLF) in adults have been made by the Asian Pacific Association for the Study of the Liver,\(^7\) North American Consortium for the Study of End Stage Liver Disease,\(^8\) American Association for the Study of Liver Diseases/ European Association for the Study of the Liver,\(^9\) and the European Association for the Study of the Liver-Chronic Liver Failure Consortium.\(^10,11\) All studies focused on adult diseases, principally alcoholic liver disease, nonalcoholic liver disease, and chronic hepatitis C. Diversity of diagnostic criteria for ACLF also complicates clinical studies in this area.\(^12\) Characterization of ACLF in children is lacking to the degree that evidence-based recommendations cannot be made at this time, but should be explored given distinct differences in etiology and pathophysiology that exist between adult patients and children with ACLF.

**METHODS**

The PODIUM collaborative sought to develop evidence-based criteria for organ dysfunction in critically ill children. The present article reports on the systematic review on acute liver dysfunction scoring tools performed as part of PODIUM, provides a critical evaluation of the available literature, proposes evidence-based criteria for acute liver dysfunction in critically ill children, as well as recommendations for future research. The PODIUM Executive Summary details Population, Interventions, Comparators, and Outcomes questions, search strategies, study inclusion and exclusion criteria, and processes for risk of bias assessment, data abstraction and synthesis, and for drafting and developing agreement for criteria indicating acute liver dysfunction.\(^13\)

**RESULTS**

Of the 7546 unique citations published between 1992 and 2020, 54 studies were eligible for inclusion, as shown in the PRISMA flowchart (Fig 1). Data tables (Supplemental Tables 1 and 2) and risk of bias assessment summaries (Supplemental Fig 1) are detailed in the Supplemental Information. Criteria for acute liver dysfunction in critically ill children informed by the evaluated evidence are listed in Tables 1–3.

The PODIUM hepatology subgroup performed data extraction on 22 prospective and 24 retrospective articles as well as on 8 articles felt to provide important clinical merit. Most participants in these studies were enrolled in the pediatric intensive care unit (PICU), but individuals meeting clinical criteria outside the PICU were included. Before 2006, criteria for study entry were varied and included those listed for a liver transplant for acute
hepatic necrosis or acute liver failure, clinical diagnosis of acute hepatic dysfunction, or meeting KCHC. However, after the initial report by the Pediatric Acute Liver Failure Study Group, almost 90% of subsequent national and international reports, both retrospective and prospective, of acute liver failure in children used PALF study entry criteria to identify their study cohort.

To meet PALF criteria, a patient must have no history of chronic liver disease. Urgency to establish PALF requires a careful history and physical examination to establish, as best as possible, that the child does not have a known chronic liver disease. If history reveals previous episodes of jaundice, elevation of liver tests, or a known liver diagnosis, then an underlying chronic liver disease should be explored as acute decompensation of a chronic liver disease can present similar to ALF. Likewise, findings on physical examination such as digital clubbing in the absence of chronic lung or cardiac disease, prominent submucosal abdominal blood vessels, or clinically apparent ascites before intravenous fluid administration could be features of chronic portal hypertension that suggest an underlying chronic liver disease. In the absence of these features in a previously healthy child, absence of a known chronic liver disease should be assumed.

Specific cut-points for biochemical evidence of liver injury were not incorporated into the PALF criteria because some liver tests may be in the normal or minimally elevated range for some presenting with ALF. For instance, patients with acetaminophen toxicity are typically not jaundiced at presentation and their total bilirubin can be in the 2 to 3 mg/dL range which is typically below a level at which jaundice is clinically detectable. Likewise, children with tyrosinemia, galactosemia, or gestational alloimmune liver disease (formerly neonatal iron storage disease) can present with aminotransferase levels <1.5 times the upper limit of normal. However, we recognize the need for laboratory parameters that are generally agreed to be consistent with acute liver injury to minimize variability in interpretation and also captured in the electronic medical record. Therefore, in the referenced articles, median and range values of liver test abnormalities in various PALF populations (eg, infant <90 days, indeterminate, acute and chronic...
Coagulopathy in the setting of PALF is complex, but readily available laboratory parameters are needed to indicate impaired liver function. European studies initially used a depressed level of factor V to establish liver failure. Other investigators calculated prothrombin activity, using values <50% and <40% of normal to determine evidence of hepatocyte dysfunction. The PALF study group used prothrombin time (PT) and the INR as markers of hepatocyte synthetic dysfunction because 1 or both were universally available and resulted within hours. Recent data suggest that elevated PT and INR in ALF is not associated with bleeding risk but is rather more indicative of hepatocyte dysfunction. Vitamin K administration does not improve coagulopathy in liver disease in the absence of nutritional deficiency, but it does reverse vitamin K deficiency because of malabsorption or warfarin toxicity. As "Day 1" of ALF is rarely known (exception is acute acetaminophen single dose poisoning), subclinical liver insufficiency may result in a degree of vitamin K deficiency due to malabsorption. This is demonstrated by reduction in INR in some individuals with ALF after vitamin K administration. Patients with nutritional deficiency or malabsorption of vitamin K will typically experience rapid and near normalization of PT and INR with parenteral administration of vitamin K. Evidence to establish a precise time interval between vitamin K administration and improvement in INR is more robust in patients with asymptomatic warfarin toxicity. INR response to vitamin K is more predictable when given intravenously rather than subcutaneously. Improvement in INR begins almost immediately after intravenous administration of 1 mg of vitamin K in patients with warfarin toxicity. If the response to vitamin K drops the INR less than a critical level (eg, INR <2 without clinical hepatic encephalopathy [HE] or <1.5 with clinical HE), then the patient would not meet criteria for ALF. Alternatively, if the INR remains greater than the thresholds

Table 1: PODIUM: Criteria for Acute Liver Dysfunction in Critically Ill Children

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Criterion for Organ Dysfunction</th>
<th>Suggested Thresholds</th>
<th>Conditions</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>aspartate aminotransferase</td>
<td>&gt;100 IU/L</td>
<td>Absent hemolysis or myopathy</td>
<td>Not graded</td>
</tr>
<tr>
<td>Liver</td>
<td>alanine aminotransferase</td>
<td>&gt;100 IU/L</td>
<td>Absent hemolysis or myopathy</td>
<td>Not graded</td>
</tr>
<tr>
<td>Liver</td>
<td>γ-glutamyl transpeptidase</td>
<td>&gt;100 IU/L</td>
<td>Absent biliary obstruction</td>
<td>Not graded</td>
</tr>
<tr>
<td>Liver</td>
<td>Total bilirubin</td>
<td>&gt;5 mg/dl (&gt;85.5 μmol/L)</td>
<td>Absent suspected Gilbert’s Disease</td>
<td>Not graded</td>
</tr>
<tr>
<td>Liver</td>
<td>Direct or conjugated bilirubin</td>
<td>&gt;2 mg/dl (&gt;34.2 μmol/L)</td>
<td>Absent biliary obstruction</td>
<td>Not graded</td>
</tr>
<tr>
<td>Liver and Coagulation</td>
<td>PT ≥ 15 s or INR ≥ 1.5 after vitamin K administration</td>
<td>IR between 1.5-1.9 encephalopathy must be present. INR ≥ 2 encephalopathy not required</td>
<td>To ensure vitamin K deficiency is not a principal component of the coagulopathy, a single dose of intravenous vitamin K (1 mg for infants up to 10 mg in adults) is administered with repeat PT/INR determined 6-8 h later.</td>
<td>Not graded</td>
</tr>
<tr>
<td>Liver and CNS</td>
<td>Table 1 children &lt;3 y</td>
<td>NA</td>
<td>Must be present if INR between 1.5 and 1.9; should be assessed if INR ≥ 2</td>
<td>Grade I/II, III, and IV</td>
</tr>
<tr>
<td>Liver and CNS</td>
<td>Table 2 children 3–18 y</td>
<td>NA</td>
<td>Must be present if INR between 1.5 and 1.9; should be assessed if INR ≥ 2</td>
<td>Grade I to IV</td>
</tr>
</tbody>
</table>

Precondition for all criteria: no known evidence of chronic liver disease with duration of acute symptoms <8 wk and biochemical evidence of acute liver injury if any laboratory value is present.

Wilson disease is an exception as severe Coombs-negative hemolysis may be present. CNS, central nervous system; PT, prothrombin time.

Table 2: Hepatic Encephalopathy Grading Scale (for Patients Under 5 Years of Age)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical</th>
<th>Asterixis/Reflexes</th>
<th>Neurologic Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (I and II)</td>
<td>Inconsolable crying, sleep reversal, inattention to task</td>
<td>Unreliable/normal or hyperreflexic</td>
<td>Unreliable/normal or hyperreflexic</td>
</tr>
<tr>
<td>Mid (III)</td>
<td>Somnolence, stupor, combative ness</td>
<td>Unreliable/hyperreflexic</td>
<td>Unreliable/hyperreflexic</td>
</tr>
<tr>
<td>Late (IV)</td>
<td>Comatose, arouses with painful stimuli (IVa), or no response (IVb)</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

outlined after administration of vitamin K, the patient meets PALF criteria. Clinical practice in PALF is to use 1 mg (infants) up to 10 mg (adults), depending on the age of the patient. One should expect improvement in INR within 6 to 8 hours of vitamin K administration. We recognize that vitamin K administration would not correct coagulopathy associated with disseminated intravascular coagulation. Further research is needed to better characterize clinical and hematologic differences in the coagulation profile associated with disseminated intravascular coagulation and ALF.

Clinical HE is an essential component of ALF in adults. Despite difficulty assessing children with HE, particularly younger ones, HE must also be incorporated into the clinical criteria for PALF because its presence and trajectory are associated with outcomes, including liver transplant and death.\textsuperscript{5,6} Characterization of HE for entry into the PALF study used 2 grading scales. The Whittington Scale (Table 2) is used for children < 3 years of age\textsuperscript{29} and the West Haven Criteria for those between 3 to 18 years of age (Table 3).\textsuperscript{29} Of 54 studies reviewed, 6 used study criteria that included the onset of HE within 4 or 8 weeks of either jaundice or other symptoms. Unfortunately, HE, jaundice onset, and other symptoms are subjective and highly dependent on the observer and reporter. Therefore, there is likely a significant degree of uncertainty and variability when making precise determinations of when symptoms and HE began. It remains important to include HE in the inclusion criteria and should be present when the liver-based coagulopathy is modest (eg, uncorrectable INR between 1.5 to 2.0) as changes in HE (improvement, worsening, persistence, and fluctuation) are associated with outcome.\textsuperscript{5,6} Whereas participants without clinical evidence of HE at enrollment but an INR >2.0 were included in the PALF study, 30% of those subjects had clinical progression of HE in the 7 days after enrollment and were more likely to receive a liver transplant.

CONCLUSIONS

After the initial report of the Pediatric Acute Liver Failure Study Group,\textsuperscript{4} 25 national and international studies have used the PALF study entry criteria proposed above to identify a cohort to examine whether a variety of disease severity scores or biomarkers are able to predict outcomes, including transplant, death, and recovery. Ideally, a marker of disease severity would be one that would predict death and identify those at greatest need for a liver transplant. In the pretransplant era, there were only 2 outcomes: death and survival with native liver. In the current era where liver transplant is a treatment option, it is important to recognize that receiving a liver transplant interrupts the natural history of PALF. Therefore, the transplant cohort is heterogeneous and composed of those who would have lived and those who would have died had they not received a liver transplant. Unfortunately, virtually all studies seeking to identify parameters to predict outcome are flawed when death and liver transplant are combined into a single outcome for data analysis.

PALF study entry criteria were not intended to predict outcome. During the course of the PALF study, we found that neither KCHC\textsuperscript{30} nor the Liver Injury Unit Score\textsuperscript{31} satisfactorily predicted death in the PALF study cohort. Because the course of PALF is dynamic, use of multiple clinical and biochemical

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical</th>
<th>Asterisks/Reflexes</th>
<th>Neurologic Signs</th>
<th>EEG Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>None/normal</td>
<td>Psych testing only</td>
<td>Normal</td>
</tr>
<tr>
<td>I</td>
<td>Confused, mood changes, altered sleep habits, loss of spatial orientation, forgetful</td>
<td>None/normal</td>
<td>Tremor, apraxia, impaired handwriting</td>
<td>Normal or diffuse slowing to 0 rhythm, triphasic waves</td>
</tr>
<tr>
<td>IIa</td>
<td>Drowsy, in appropriate behavior, decreased inhibitions</td>
<td>None/hyperreflexic</td>
<td>Dysarthria, ataxia</td>
<td>Abnormal generalized slowing, triphasic waves</td>
</tr>
<tr>
<td>IIIa</td>
<td>Stuporous, obeys simple commands</td>
<td>None/hyperreflexia, up going toes (1 Babinski)</td>
<td>Rigidity</td>
<td>Normal generalized slowing, triphasic waves</td>
</tr>
<tr>
<td>IV</td>
<td>Comatose, arouses with painful stimuli (I Va), or no response (IVb)</td>
<td>Absent</td>
<td>Decerebrate or decorticate</td>
<td>Abnormal, very slow δ activity</td>
</tr>
</tbody>
</table>

*Patients with clinical assessment of HE who were subsequently intubated were assessed as having Grade III–IV, unless other neurologic signs (eg, decerebrate or decorticate posturing) were present allowing for a more specific HE classification. Those without a HE assessment before intubation were not classified. Adapted from Ng VL, Li R, Loomes KM, et al; Pediatric Acute Liver Failure Study Group (PALFSG). Outcomes of children with and without hepatic encephalopathy from the pediatric acute liver failure study group. J Pediatr Gastroenterol Nutr. 2016;63(3):357–364.
measures at and after admission will likely identify those who meet PALF entry criteria after hospital admission as well as guide treatment and liver transplant decisions. Utilizing the trajectory of total bilirubin, INR, and HE over 7 days after study entry, we were able to identify 5 distinct patterns associated with outcomes that may have important prognostic value.6

Among outcomes at 21 days in 1041 participants having met PALF study criteria, 529 (51%) were alive with native liver, 178 (17%) were dead, and 334 (32%) received a liver transplant 21 days after study entry.19 For those meeting PALF entry criteria, outcomes of survival with native liver, liver transplant, and death occurred across all age groups and diagnostic categories as well as those enrolled with an uncorrectable coagulopathy in the absence of encephalopathy.5 Therefore, meeting these criteria does not presume imminent death or absolute need for liver transplant. Rather, the criteria identify an infant, child, or adolescent who has reached a clinical threshold where all 3 outcomes are possible and should, at the very least, prompt an urgent discussion and liaison with a recognized pediatric liver transplant center regarding timely transfer for liver transplant evaluation if liver failure is the principal driver of multiorgan dysfunction.

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REFERENCES


ABBREVIATIONS

ACLF: acute-on-chronic liver failure
ALF: acute liver failure
CNS: central nervous system
HE: hepatic encephalopathy
INR: international normalization ratio
KCHC: Kings College Hospital criteria
PALF: pediatric acute liver failure
PICU: pediatric intensive care unit
PODIUM: Pediatric Organ Dysfunction Information Update Mandate
PT: prothrombin time

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