Proceedings of ESPGHAN Monothematic Conference 2020: “Acute Liver Failure in Children’: Diagnosis and Initial Management

**ABSTRACT**

**Objectives:** The Hepatology Committee of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) aims to educate pediatric gastroenterologists, members of ESPGHAN and professionals from other specialties promoting an exchange of clinical expertise in the field of pediatric hepatology. Herewith we have concentrated on detailing the recent advances in acute liver failure in infants and children.

**Methods:** The 2020 ESPGHAN monothematic three-day conference on pediatric hepatology disease, entitled “acute liver failure” (ALF), was organized in Athens, Greece. ALF is a devastating disease with high mortality and most cases remain undiagnosed. As knowledge in diagnosis and treatment of ALF in infants and children has increased in the past decades, the objective was to update physicians in the field with the latest research and developments in early recognition, curative therapies and intensive care management, imaging techniques and treatment paradigms in these age groups.

**Results:** In the first session, the definition, epidemiology, various causes of ALF, in neonates and older children and recurrent ALF (RALF) were discussed. The second session was dedicated to new aspects of ALF management including hepatic encephalopathy (HE), coagulopathy, intensive care interventions, acute on chronic liver failure, and the role of imaging in treatment and prognosis. Oral presentations by experts in various fields are summarized highlighting key learning points.

**Conclusions:** The current report summarizes the major learning points from this meeting. It also identifies areas where there is gap of knowledge, thereby identifying the research agenda for the near future.

**Key Words:** etiology, hepatic encephalopathy, imaging, intensive care

(JPGN 2022;74: e45–e56)
Acute liver failure (ALF) is a rare condition in children, characterized by massive loss of hepatic parenchyma secondary to liver injury, and is associated with significant morbidity and mortality (1,2). Initial care is challenging, mainly supportive and requires numerous clinical investigations to establish a diagnosis, while most children may remain undiagnosed. Liver transplantation (LT) is frequently required and timely implementation has improved survival.

The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Hepatology Committee organized 3-day monothematic conference, on “advances in acute liver failure” in infants and children on January 30–February 1, 2020, in Athens, Greece bringing together experts in the fields of hepatology, intensive care, radiology, hematology, immunology and surgery and trainees in pediatric hepatology. The conference aimed to address diagnostic and treatment dilemmas, identify gaps in knowledge and pose clinical questions for future research.

The program is listed in Table 1. and the present article focuses on sessions 1 and 2. In the first session, the definition, epidemiology, various causes of ALF, in neonates and older children and recurrent ALF (RALF) were discussed. The second session was dedicated to new aspects of ALF management including hepatic encephalopathy (HE), coagulopathy, intensive care interventions, acute on chronic liver failure, and the role of imaging in treatment and assessment of the prognosis.

**SESSION 1. ACUTE LIVER FAILURE: ETIOLOGY AND DIAGNOSTIC APPROACH**

**Definition and Epidemiology: Where Do We Stand?**

In 1999, the pediatric ALF study group (PALFSG) was established including 21 pediatric liver centers across North America and the United Kingdom (1). The PALFSG established study entry criteria as having biochemical evidence of acute liver injury, with no known evidence of prior liver disease, with persistent coagulopathy after vitamin K, and with clinical encephalopathy (required if international normalized ratio [INR] 1.5–1.9, but not necessary if INR > 2.0). As illustrated in Table 2, the cause in over 1000 PALF patients was indeterminate in 42% while acetaminophen toxicity was the most frequent specific diagnosis in 14% (3,4).

Indeterminate PALF (iPALF) is a heterogeneous cohort and the most common among all age groups, partly due to incomplete investigations. In other cases, the diagnosis may not have been considered, due to investigations being not age appropriate, blood sampling limitations or unrecognized drug ingestion. Another challenge, is the possible involvement of an unknown metabolic or genetic defect or virus as well as in some cases an undiagnosed underlying immune dysregulation (autoimmune positive markers, gestational alloimmune liver disease (GALD), natural killer cell dysfunction etc.) (5).

In order to address issues related to incomplete diagnostic testing, a learning collaborative approach was utilized to identify and implement age-specific diagnostic tests at each PALF site (4). Age-specific diagnostic testing resulted in a decrease of prevalence of iPALF across all age groups. In the neonatal group, more viral and GALD diagnoses were established and in the middle age group more metabolic liver disease and non-acetaminophen induced drug injury whilst in older children haemophagocytic lymphohistiocytosis (HLH) and acetaminophen induced-ALF cases were more common. Reduction in iPALF was accompanied by a decrease in liver transplantation without an increase in mortality (4).

Screening tests for underlying diagnoses are used to prioritize more specific diagnostic tests, but are often non-specific. For instance, elevated lactate/pyruvate ratios were found not to be diagnostic of mitochondrial disease (6) and the presence of serum autoantibodies was insufficient for a diagnosis of autoimmune disease (7). If next-generation sequencing with results available in time to influence clinical decision making was incorporated into diagnostic algorithms of PALF, this is an important first step in diagnosis (8).

Outcomes in 944 out of 1044 PALF participants were classified by diagnosis, iPALF (n = 418), N-acetyl-p-aminophenol-paracetamol (APAP) toxicity (n = 114), metabolic n = 98), autoimmune (n = 64), viral (n = 73), drug (n = 27), iron storage disease (n = 25), HLH (n = 22), other (n = 102) and showed that patients with iPALF had a higher rate of LT. Death was the outcome in 119 children, LT occurred in 280 (30%) children and overall, 545 of 944 (58%) children survived ALF with their native liver. As liver transplantation interrupts the natural history of PALF, efforts to reliably predict outcomes remain a critical challenge. Therefore, using a growth mixture model with dynamic trajectories of INR, total bilirubin and encephalopathy over time, (7–21 days, in 380 participants following PALF enrolment), led to identification of five latent subgroups associated with outcome. Among the various groups, the group of patients with low INR, low serum bilirubin, without encephalopathy survived without LT. The group with high and increasing INR and serum bilirubin, and slowly developing encephalopathy should be considered early for LT (9).

Overall, the PALF study recognized the need for a correct diagnosis and the timely identification of those at risk for death or LT. Further quality of diagnostic testing is needed to establish an etiology in the iPALF cases. Minimizing heterogeneity within the indeterminate cohort of patients will improve LT utilization, and provide the opportunity to discover novel diagnoses potentially amenable to targeted therapy.

**Acute liver failure in neonates and infants**

ALF may occur at any age, with a large prevalence in infancy before one year of age (1). Diagnosis of ALF in neonates and infants is difficult because jaundice is not a consistent finding, HE is often a late event and difficult to diagnose, and some infants may die without HE. On the other hand, encephalopathy may not result from liver failure, but from underlying metabolic defects such as defects in the urea cycle, and fatty acid oxidation defects.

The management of young children with ALF mandates a multidisciplinary approach and intense monitoring. Among 107 infants below 1 year of age managed for ALF in Bicêtre Hospital in

---

**Address correspondence and reprint requests to Aglaia Zellos, MD, PhD, First Department of Pediatrics, National and Kapodistrian University, Aghia Sophia Children’s Hospital, Thivon and Lepadias Street, 11527 Athens, Greece (e-mail: agli.zellos@gmail.com).

The authors report no conflicts of interest.

**Disclaimer:** Although this paper is produced by the ESPGHAN Hepatology Committee, it does not necessarily represent ESPGHAN policy and is not endorsed by ESPGHAN.

**Copyright © 2021 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition.

**DOI:** 10.1097/MPG.0000000000003341

---

**Copyright © ESPGHAN and NASPGHAN. All rights reserved.**
Contraindications to LT were related to the underlying cause of ALF in 65% of cases, including mitochondrial disorders, leukemia, HLH, to irreversible brain damage in 13% and to multi-organ failure in 22% (10). This clearly highlights that neonates and infants with ALF should be managed in pediatric liver transplant centers, to urgently attempt to identify the etiology of ALF, to assess conditions treatable without LT and determine whether there are contraindications to LT. Interventions with supportive care measures are required to prevent and treat complications of ALF and decide on the appropriate time for LT, before multi-organ liver failure and irreversible neurologic damage occurs.

France over a 20-year period, 26% recovered without LT, 32% underwent an emergency LT, 5% died while waiting for LT and 37% were not listed for LT because of contraindications and died (10). The main causes of ALF in neonates and infants are listed in Table 3 (4,10). Among these, viral infections and inborn metabolic disorders are the most common causes. However, the proportion of iPALF remains high, (20% <3 months, 50% between 3 months–3 years), despite implementing a recommended age-specific diagnostic test screening at the time of hospital admission (4). With the implementation of genetic studies, the recognition of new causes of ALF, or recurrent ALF (RALF) in infancy, is increasing (8). The most common cause of ALF in neonates is now recognized as GALD. GALD is an alloimmune process, where maternal alloantibody activates fetal complement cascade to produce a membrane attack complex and fetal liver injury. GALD can be treated by an early exchange transfusion and intravenous immune globulin (IVIG), allowing transplant-free survival in up to 80% of patients.
cases (11). If GALD is not treated timely, the outcome is poor (>90% mortality). In case of death, a liver biopsy should be performed to confirm the diagnosis, since treatment with high-dose IVIG in subsequent pregnancies at risk for GALD effectively prevents poor outcome (11).

ALF later in neonatal age may be related to a bacterial or viral infection or a metabolic condition unveiled by the introduction of feeding. Most metabolic diseases such as galactosemia, hereditary fructose intolerance, tyrosinemia type 1, urea cycle defects, fatty oxidation defects, are treatable with an appropriate diet and specific therapy, although the first presentation of the disease may already have caused irreversible damage. Upon suspicion, feeds should be withheld until the results of metabolic screening are available and this may reverse ALF. The most frequent viral-induced ALF in neonates is herpes simplex and high dose intravenous acyclovir needs to be started as early as possible until results of screening.

Diagnostic hints may point to a specific disease. Sodium valproate induced liver failure may unmask a mitochondrial disorder, due to an underlying mutation in mitochondrial DNA polymerase gamma (pol gamma), (POLG), and is generally considered a contraindication to LT. Encephalopathy, high plasma ammonia but mild coagulopathy and no jaundice may point to urea cycle defect (UCD). Splenomegaly and thrombocytopenia are noted in leukemia and HLH and a bone marrow smear should be performed. Anemia may indicate Parvovirus B19, autoimmune giant cell hepatitis or leukemia.

Conditions that are not cured by LT must be identified early such as HLH, leukemia, Niemann-Pick C, mitochondrial diseases with multisystem involvement in cases of POLG, MPV17, valproic acid-induced ALF-POLG (12). In patients with mitochondrial diseases without evidence of neurological involvement, the decision to proceed with or refrain from LT is very challenging, as some patients may not develop neurological deterioration. Thorough evaluation at

| TABLE 2. Final diagnosis in 986 PALF study participants |
|---------------------------------------------|-----------------|-----------------|-----------------|
| Diagnosis N (%)                           | 0–90 days (N = 181) | 91 days–3 y (N = 274) | 4–17 y (N = 531) |
| Indeterminate                             | 64 (30)          | 162 (60)         | 218 (41)        |
| Acetaminophen                             | 1 (1)            | 12 (4)           | 110 (21)        |
| Metabolic                                 | 31 (18)          | 30 (11)          | 39 (7)          |
| Galactosemia                              | 13               | 0                | 0               |
| Mitochondrial                             | 9                | 10               | 2               |
| Niemann-Pick type C                       | 4                | 0                | 0               |
| Tyrosinemia                               | 3                | 6                | 0               |
| Urea cycle defect                         | 2                | 5                | 1               |
| Fatty acid oxidation                      | 0                | 5                | 0               |
| Alpha-1 antitrypsin                       | 0                | 2                | 0               |
| Fructose intolerance                      | 0                | 1                | 0               |
| Glycogenylation defect                    | 0                | 1                | 0               |
| Wilson disease                            | 0                | 0                | 36              |
| Viral                                     | 36 (21)          | 14 (5)           | 27 (5)          |
| Herpes                                    | 28               | 1                | 2               |
| Enterovirus                               | 6                | 1                | 1               |
| Cytomegalovirus                           | 2                | 1                | 0               |
| Influenza/parainfluenza                   | 0                | 3                | 2               |
| Epstein–Barr virus                        | 0                | 3                | 5               |
| Adenovirus                                | 0                | 2                | 3               |
| Paramyxovirus                             | 0                | 1                | 2               |
| Hepatitis B                               | 0                | 1                | 2               |
| Hepatitis E                               | 0                | 0                | 2               |
| Hepatitis A                               | 0                | 0                | 5               |
| Hepatitis C                               | 0                | 0                | 1               |
| Human herpes virus 6                      | 0                | 1                | 1               |
| Parvovirus                                | 0                | 0                | 1               |
| immune mediated viral                     | 29 (16)          | 30 (11)          | 57 (11)         |
| GALD                                      | 27               | 0                | 0               |
| Autoimmune                                | 0                | 20               | 48              |
| HLH                                       | 2                | 10               | 9               |
| Other viral                               | 20 (11)          | 26 (9)           | 80 (15)         |
| Shock/ischemia                            | 6                | 8                | 17              |
| Leukemia                                  | 1                | 0                | 2               |
| Veno-occlusive disease                    | 0                | 6                | 6               |
| Non-APAP DILI                              | 6                | 2                | 27              |
| Mushroom toxicity                         | 0                | 0                | 5               |
| Budd-Chiari                               | 0                | 0                | 3               |
| Multiple diagnoses                        | 0                | 5                | 13              |
| Other                                     | 7                | 5                | 7               |

APAP = acetaminophen; DILI = drug-induced liver injury; GALD = gestational alloimmune liver disease; HLH = hemophagocytic lymphohistiocytosis; PALF = pediatric acute liver failure. Adapted from Narkewicz MR, et al. Clinical Gastro Hepatol 2018 (4).
The approach to a patient with RALF includes clinical phenotyping to assess involved organ systems, age at onset and trigger, levels of ammonia, lactic acid, plasma amino acids, urine amino acids, and confirmation by genetics. Diagnosis allows specific therapeutic options in some diseases, such as in UCD (ammonia scavengers, citrulline, diet) and in DLD deficiency (vitamins B1, B2). In Cytosolic aminoacyl-tRNA synthetase deficiencies, such as in UCD (ammonia scavengers, citrulline, diet) and in DLD deficiency (vitamins B1, B2), the coating of COP or vesicle formation. There is an 110 patients with a total follow-up of 639 patient-years are known (25,26). The growing number of patients has demonstrated that NBAS variants cause multiple phenotypes depending on the genotype. Three phenotypic subtypes can be differentiated: "combined phenotype", "infantile liver failure syndrome type 2 (ILFS2)", and "Short Stature, Optic atrophy and Pelger Huet anomaly syndrome (SOPH syndrome)". RALF is typically triggered by febrile disease, with most severe episodes around 2–3 years of age and decreasing frequency with age (23,26–28).

The approach to a patient with RALF includes clinical phenotyping to assess involved organ systems, age at onset and trigger, levels of ammonia, lactic acid, plasma amino acids, urine amino acids, and confirmation by genetics. Diagnosis allows specific therapeutic options in some diseases, such as in UCD (ammonia scavengers, citrulline, diet) and in DLD deficiency (vitamins B1, B2). In Cytosolic aminoacyl-tRNA synthetase deficiencies, such as in UCD (ammonia scavengers, citrulline, diet) and in DLD deficiency (vitamins B1, B2), the coating of COP or vesicle formation. There is an 110 patients with a total follow-up of 639 patient-years are known (25,26). The growing number of patients has demonstrated that NBAS variants cause multiple phenotypes depending on the genotype. Three phenotypic subtypes can be differentiated: "combined phenotype", "infantile liver failure syndrome type 2 (ILFS2)", and "Short Stature, Optic atrophy and Pelger Huet anomaly syndrome (SOPH syndrome)". RALF is typically triggered by febrile disease, with most severe episodes around 2–3 years of age and decreasing frequency with age (23,26–28).
Drug-induced Liver Injury and Toxins

Acute drug-induced liver injury (DILI) is caused by xenobiotics such as prescribed or over-the-counter drugs, illegal drugs, or herbal drugs within complementary medicine or toxins. DILI accounts for approximately 15% of all cases with PALF, according to the PALFSG and the Bicêtre center study (1,10). The prevalence varies with age and to a certain extent also with the geographic area (29).

All other causes of ALF must be ruled out, that is, infectious, immunological, metabolic, vascular etc. Relevant chronology may be investigated as symptoms and clinical signs are often not matched. Liver histology—if possible—may be helpful in some cases. Types of DILI by histology demonstrate either a hepatocellular, cholestatic or mixed hepatocellular-cholestatic type (31). Compared to adults, outcomes are better and the need for emergency LT is somewhat lower in children and adolescents. This discrepancy may be related to differences in the maturity of cytochrome P450 (CYP) systems and also to the fact that mixed intoxications are more common in adults.

APAP intoxication is the single most common drug involved in PALF, particularly in teenagers (1); however, the need for acute LT is less in adolescents compared to adults. APAP is 90% water-soluble and 5% is metabolized by p450 to the toxic metabolite N-acetyl-p-benzoquinone imine, NAPQI, which is the target of the antidote N-acetyl cysteine (NAC), converting it to the nontoxic cysteine and mercapturic acid conjugates. Interestingly, the severity of APAP intoxication (liver damage and symptoms) is more influenced by the time to start NAC than the dose used (30). Also, previous use of drugs known to enhance the effect of cytochrome P450 enzymes may increase the hepatotoxic effect.

The most common groups of other drugs causing PALF are antibiotics and antiepileptics (32). For the more commonly used antibiotics, the incidence of severe DILI is low, but the number of cases is not negligible due to an overall high consumption in children. This includes, for example, the cloxacillins, macrolides, and clavulanic acid. The mechanism through which these drugs induce DILI caused by these drugs is immune-mediated and therefore dose independent. Effects are well described in adults, but the incidence in children is unknown. There is often a cholestatic clinical presentation, with onset can be days-weeks after treatment is finished, with possible HLA linkage in children (33). Fluoxacillin has a similar pattern and may cause severe, HLA linked toxicity. Erythromycin and azithromycin have a similar pattern with tendency for skin reactions. For less commonly used antibiotics, such as isoniazid and minocycline, the incidence of drug-induced PALF may be higher.

Among antiepileptics causing DILI, valproate acid, which is a commonly used compound, is associated with a risk of PALF, in particular, if there is an underlying mitochondrial disease. In fact, it is suggested that initiation of valproate should require testing for mutations causing mitochondrial diseases, such POLG mutations.

Drugs other than those prescribed by physicians cause a proportion of DILI and illicit drugs, in particular potent sympathomimetics, which can cause multiorgan failure, including PALF (34). Herbal drugs may be activated by CYP450 system. Recreational drugs such as marijuana cause acute hepatitis, while ingestion of the toxin of Amanita phalloides causes PALF.

Currently, there is no available biomarker to distinguish DILI from the severe liver disease or other causes (35). Improved use of available notification systems and multicenter networks for DILI are important tools to enhance our knowledge in this field (32).

ACUTE LIVER FAILURE AND IMMUNE DYSREGULATION

There is a remarkable similarity between the presentation of PALF and pediatric HLH, which often progresses in ALF. To establish the diagnosis of HLH, either molecular diagnosis and/or 5 of 8 from the following criteria must be present: fever, splenomegaly, cytopenias, hypertriglyceridemia, and/or hypofibrinogenemia, hemophagocytosis in bone or spleen of lymph node, low or absent natural killer (NK) cell activity, ferritin >500 mcg/L and soluble CD25 (interleukin [IL]-2 receptor) > 2400 U/mL (36); however, they are still limited and outdated. The traditional classification of primary/genetic HLH is divided into the familial HLH disorders (FHL) (labeled from 1 to 5) and those associated with primary immunodeficiencies (PID), such as Chediak Higashi, Griscelli syndrome, XLP, XIAP deficiency, where the incidence of HLH is increased. X-linked lymphoproliferative disorder (XLP), or SAP deficiency involves a mutation in SH2D1A, which encodes a SLAM associated protein deficiency (37). Younger patients with HLH are more likely to have a monogenic intrinsic defect and older patients may have been triggered by various antigenic challenges such as infection, autoimmunity and hematologic malignancy leading to immune hyper inflammation. A number of genetic defects and metabolic disorders caused by different pathogenic mechanisms (impaired lymphocyte cytotoxicity, dysregulated inflammasome activity, dysregulated metabolism, impaired autophagy and control of viruses) render predisposition to HLH (38,39).

A diagnostic algorithm is used to detect triggers, familial HLH and PID, starting with first-line investigations, such as HLH biomarkers (blood count, coagulation screen, ferritin, LDH, triglycerides, liver function, soluble CD25, Bone marrow aspirate, lumbar puncture (EBV viral load, protein, cytology), rheumatology (ANA, dsDNA, c3,c4, urine albumin/creatinine), virology (CMV, HSV, VZV, HHV6,7, parvovirus, HIV, EBV DNA in blood, CSF, tissues, BM, EBV serology, and titers), immunophenotype, functional immunology (T-proliferative responses, cytokotoxic granular release assay, DHR/NBT), genetics (targeted Sanger sequencing for EBV-susceptible PID and HLH genes), histopathology (hair shaft for microscopy, BM biopsy), and protein expression (perforin, WASp, SAP, XIAP, ITK). Second-line investigations include further genetic testing (NGS, WES/WGS sequencing), microbiology (toxoplasmosis, Leishmaniasis, adenovirus, mycoplasma, Brucella, malaria, Rickettsial infection, Bartonella), further immunology and protein expression testing (soluble CD25, flow cytometry (perforin expression, granule release assay, SAP and XIAP expression if male), DNA-activate genetic), as well as EBV (typing and EBV latency stage determination).

Treatment of HLH includes dexamethasone, cyclosporine, VP-16 and if EBV positive rituximab. Hematopoietic stem cell transplantation (HSCT) for genetically proven primary HLH is performed as early as possible while management is conservative for secondary HLH. According to the HLH 2004 treatment, results (n = 369 patients, 46% with proven primary HLH) showed overall 5-year survival 62%, pre-HSCT mortality was 20% (primary 17%). Progression to HSCT occurred in 51% of patients with 60% 5-year survival, an identical outcome when compared to the 1994 HLH treatment protocol (40). Personized treatment is now leading the way using targeted T cell lytic therapies (CAMPATH, ATG),...
specific biologics (Emapalumab, Anakinra, IL18 binding protein), target HSCT to specific disorders, and gene therapy.

In conclusion, as primary immunodeficiency may underlie a child with ALF (ie, primary HLH, autoimmune hepatitis), diagnosis is difficult to establish, without specialist immunology laboratories.

Infections and Acute Liver Failure

Infections are the leading cause of PALF in low and middle-income countries (41,42). In these countries, the lack of effective water sanitation facilities, of hygienic requirements for food processing and a sound sanitary system with adequate vaccination programs is responsible for the high incidence of hepatitis A virus (HAV) and hepatitis E virus (HEV) infections. The risk of developing ALF with HAV infection is <1% but increases in patients with underlying chronic liver disease (41,42). In western countries, acute hepatitis due to HEV is most frequently seen in patients who recently traveled to endemic areas, although sporadic cases are detected. The risk of developing ALF with HEV infection in adults is <3%. While hepatitis C virus has not been reported as a cause of PALF, HBV could cause PALF due to either acute hepatitis or reactivation in immunosuppressed children (42,43). Reactivation of HBV is a known complication of immune-suppressive therapies and has been defined as a sudden increase in HBV DNA level or the de novo detection of HBV DNA viremia whenever undetectable before the initiation of the immune-suppressive, cytotoxic, or biological modifier therapy irrespective of alanine aminotransferase level and of HBsAg reverse seroconversion (43). The clinical course of HBV reactivation is unpredictable and ranges from mild hepatitis to liver failure and even death. Reactivation of HBV is preventable or amenable to treatment with the appropriate use of antivirals. Screening for HBV infection is therefore essential before LT and/or significant immunosuppression.

In the United States and Western Europe, hepatitis A, B and C are often suspected but seldom identified as the etiology for PALF. According to PALFSG, viral infections account for up to 9% of the cases of PALF in high-income countries (3). The prevalence and the prognosis vary with the age of the child. In neonates, many viruses of the herpes family, as well as enterovirus, adenovirus and parvovirus have been identified as causes of PALF and are associated with higher mortality rate compared to infants and older children (44). Initiation of treatment with high-dose parenteral acyclovir improves survival and the long-term neurological outcome. LT has been successful in stable neonates with HSV infection (45). Outside the neonatal period, a variety of viruses have been reported to cause PALF. HSV 1 and 2, varicella-zoster, Cytomegalovirus, Epstein–Barr virus, human herpesvirus-6, 7, and 8, enterovirus, parvovirus, adenovirus, rubella and paramyxovirus and, in endemic countries, Dengue and yellow fever have been associated with PALF. Even though these infections are more commonly seen in immunosuppressed patients, they may also occur in immunocompetent children (3).

Overall, it is difficult to predict the prognosis in neonates and children with ALF of infectious etiology. A study by the PALFSG analyzed the cumulative mortality without transplantation at up to 21 days post-enrollment in neonates and infants ages <90 days showing that young infants with a viral etiology had the highest mortality risk and were least likely to receive LT (44). Viral induced multi-organ failure often renders these patients poor transplant candidates. The presence of a disseminated viral infection would also be a relative contraindication to the significant immunosuppression required in the immediate post-operative period (45).

Screening of blood for the viruses that could possibly be responsible of PALF should be undertaken in all patients, where the etiology of PALF is not clear by using nucleic acid testing and serology. The ubiquitous nature of viruses and confounding exposure to potentially hepatotoxic medications make it difficult to invoke a cause-and-effect of the identified virus at the time of clinical presentation and to establish the role of the virus as a primary agent or as a co-factor.

Non-viral infections such as malaria, leptospirosis and rickettsiosis may result in PALF, albeit uncommonly. Furthermore, children with PALF are at increased risk of developing infections, sepsis and septic shock. Infectious complications were a leading cause of death in ALF in adults, with bacterial infections documented in 60–80%. Surveillance cultures should be performed to detect bacterial and fungal infections as early as possible and prophylactic broad-spectrum antibiotics and antifungals should be started in all children and acyclovir should be administered to neonates, infants and immunosuppressed patients. The role of infectious agents as primary causes of ALF or as cofactors needs to be carefully evaluated case-by-case and a positive serology or molecular method result should not exclude a careful and extensive diagnostic work up for other underlying causes of liver disease.

SESSION 2. ACUTE LIVER FAILURE: INITIAL MANAGEMENT DILEMMAS

Hepatic Encephalopathy

The management of a child admitted for ALF and HE represents a challenge for the pediatric intensivist and hepatologist. The progression of the disease may be rapid and severe neurologic complications may appear before LT could be performed (46). The pathogenesis of HE is multifactorial and not completely understood. Neurotoxins, in particular ammonia, play a crucial role. Hyperammonemia induces cerebral edema, impairs brain energy metabolism, alters neurotransmission and induces mitochondrial dysfunction. The inflammation secondary to the liver disease and bacterial translocation contributes to the brain damage, notably because of the multiorgan failure it provokes in severe cases. Other factors, such as drugs and abnormal levels of amino acids aggravate HE (47).

Clinical diagnosis of HE in ALF is a challenge. Scoring systems exist but are difficult to use in children on ventilator support and/or receiving sedation. Since early recognition of HE is essential, an electroencephalogram should be performed on admission and during follow-up. It allows HE classification and diagnosis of seizures, observed in 10–20% of the cases. Cerebral imaging may be useful, if another cause of coma is suspected, but is insensitive in detecting elevated intracranial pressure (ICP). Treatment adaptations based on ICP monitoring have not been proved to modify outcome and therefore should only be considered for children with grade 3–4 HE on the waiting list, if at all. The place of evoked potential, transcranial Doppler ultrasonography and neuro-biomarkers in neurologic assessment of children with HE needs further studies (48).

None of the drugs potentially able to reduce ammonia level have been shown to be superior to lactulose with or without rifaximin in ALF (49). Extracorporeal liver support (ECLS) offers potential advantages: according to the technique, it could remove protein-bound toxins or small soluble molecules, support the liver function and/or allow administration of proteins, such as coagulation factors. It may reduce mortality and improve HE in adults with ALF, but it has remained unclear whether it prevents transplantation. Larger trials are needed to determine the effect of ECLS on hard outcomes (50). The same conclusion may be drawn for children (51). Very few pediatric centers perform albumin dialysis; none of them has demonstrated evidence of benefit on hard outcomes. Continuous renal replacement therapy (CRRT) is indicated

www.jpgn.org e51
for children admitted for acute renal failure, fluid overload, severe electrolytes disorders and/or persistent acidosis. It reduces ammonia level and probably improves HE, but its best indications and settings should still be determined (52). Reduction of inflammation and toxin level might be important, but no technique should interfere with liver regeneration and anti-inflammatory processes.

HE requires prompt admission to a pediatric intensive care unit, where neuropsychiatric therapies should be started immediately. Hypothermia, steroids, and prophylactic use of antiepileptic drug have not shown any benefit.

Prognosis of HE could be improved with enhanced recognition, early intensive care management, better identification of specific transplant criteria and early LT if its indication has been set.

Coagulopathy

Most definitions of ALF include coagulopathy with INR > 1.5, as a criterion. There are very little data regarding coagulopathy in PALF. In adults with cirrhosis and ALF, the hemostatic system remains in balance, because the pro-hemostatic and anti-hemostatic processes are frequently equally affected (53,54). Indeed, bleeding in adults with ALF is rare and seldom a cause of death. In a study of 1770 patients with ALF (55), spontaneous bleeding occurred from the upper gastrointestinal tract (UGI) in 163 patients, while spontaneous intracranial bleed occurred in 10 patients, of whom FIVE died. Post-procedural bleeding occurred in 22 patients and the overall mortality associated with bleeding was very low (10/1770 patients). INRs were not different in patients that bled from those that did not bleed. However, those that bled had a significantly lower platelet count. It is however questionable whether thrombocytopenia is a direct cause of bleeding. More likely, thrombocytopenia is a reflection of systemic inflammation, which results in platelet activation and clearance (56).

Indeed, most bleeding complications in ALF (upper gastrointestinal bleeds) are likely unrelated to hemostatic failure, but rather a consequence of ‘‘stress-related mucosal disease,’’ which is directly related to intense systemic inflammation. Thus, the lack of bleeding despite the prolonged INR and the thrombocytopenia in patients in ALF is likely explained by simultaneous changes in pro- and anti-hemostatic pathways. In ALF, adequate hemostatic ability, was demonstrated by thromboelastography, whereas 8% of patients had a hypercoagulable profile. More detailed analyses showed highly elevated levels of the platelet adhesive protein VWF and decreased levels of the VWF-cleaving protease ADAMTS13, which compensates for the thrombocytopenia of ALF (57). In a large cohort of adult ALF patients, a VWF/ADAMTS13 unbalance was associated with poor outcome (58).

The prothrombin (PT)/INR is elevated in patients with ALF, but the PT/INR is only sensitive for factors VII, X, V, II, and I (fibrinogen) and reflects a defect in only these proteins. The PT is insensitive to natural anticoagulants. There is normal thrombin formation in ALF, because there is a concomitant decrease in pro- and anticoagulants (58,59). Also, patients with ALF are profoundly hypofibrinolytic and they thus have the capacity to form clots properly and are unable to break them down (58,59). In animal models of ALF intrahepatic clot formation contributes to progression of disease (60).

In summary, a hemostatic rebalance due to a concomitant decline in pro- and antihemostatic drivers characterizes ALF. There are indications of hypercoagulability, clinically evident as systemic thrombotic complications and intrahepatic clot formation. The ‘‘bleeding diathesis’’ of ALF should not be prophylactically corrected because, spontaneous, clinically significant bleeding in patients with ALF is rare, and there are no studies to substantiate goals of correction of INR or platelets. Furthermore, correction of the INR obscures a critical indicator of spontaneous recovery and prognosis. The administration of plasma, platelets and/or rFVIIa may be harmful as these interventions may promote thrombosis and aggravate liver injury.

Acute on Chronic Liver Failure

The literature on ACLF in children is scarce with most data coming from the adult experience. Currently, two definitions are used, one from Asia established in 2008 defining acute on chronic liver failure (ACLF) as acute hepatic insult manifesting as jaundice (bilirubin > 5 mg/dL), coagulopathy (INR > 1.5), complicated within 4 weeks by ascites ± encephalopathy in patients with previously diagnosed or undiagnosed chronic liver disease. Later, collaboration between centers in Europe and United States, led to the following definition, “acute deterioration of liver function in patients with cirrhosis, associated with a precipitating event and with failure of 1 or more organs and associated with high short-term mortality.” The multicenter European prospective observational study of EASL-CLIF (chronic liver failure), a Consortium of ACLF in cirrhosis, involved 1343 patients with cirrhosis from 29 units in eight European countries (61). A specific syndrome characterized by acute decompensation affecting various organ systems including liver, kidney, brain, coagulation defects, respiratory and circulatory disease was described. The short-term mortality was 28 days in >15% of cases. This led to the development of the CLIF-SOFA (CLIF-Sequential Organ Failure Assessment) score system predicting mortality (62) and depending on the specific organ systems involved. With regard to outcome 49% of patients improved, whereas 20% with high mortality risk died unless they were transplanted.

In adults, the most common precipitating factors for ACLF are bacterial infections, acute alcoholism and reactivation of HBV. The role of DILI triggering ACLF is not fully understood and in 40% of cases no precipitating factor is identified.

With regard to the pathogenesis, activation of monocytes and macrophages in ALF and in ACLF play a role in the formation of the systemic inflammatory response and in the anti-inflammatory phase that follows. In patients with chronic liver failure, a precipitating insult produces further hepatocyte damage and this results in a production of PAMPS (pathogen-associated molecular patterns) and DAMPs (damage-associated molecular patterns) and monocytes and macrophages are involved in cytokine production. In a second stage, liver Kupffer cells are activated and recruit monocytes from the bone marrow, causing damage and inflammation by production of more cytokines to other organs. At the same time, functional reprogramming, known as anti-inflammatory process, occurs to reverse this process and makes patients even more susceptible to sepsis (63,64). In children, there are few studies on ACLF listed in Table 4. To summarize, there was a male preponderance and median age around 9 years, of those presenting with ACLF as their first clinical presentation. The most common etiologies were Wilson disease, autoimmune hepatitis, and viral hepatitis A and E. The SOFA score and the CLIF-SOFA scores were applied in some studies and a higher score predicted mortality with outcomes of death or LT varying between 29% and 60%, depending on the availability of LT (64–70). The current pediatric literature is confusing as two papers reporting on acute liver failure in children included one-third of patients presenting as ACLF on the background of autoimmune liver disease, and these had a better prognosis compared to those presenting with ALF (65,66).

In conclusion, ACLF in adults is associated with high short-term mortality unless the patient is transplanted. Systemic inflammation is linked with ACLF and ALF and is a predictor of the outcome of ACLF. Pediatric data are currently limiting and confusing and more studies are needed to guide management and improve prognosis and outcomes.
The Role of Imaging in Diagnosis and Prognosis

Imaging modalities in ALF involves abdominal ultrasound, Magnetic Resonance Imaging (MRI) of the abdomen, neuroimaging and high-resolution computed tomography (CT). Neuroimaging should be considered in children with ALF, if it is going to influence management decisions (48). CT imaging in ALF is not useful for making diagnosis of early cerebral edema, but may be useful in diagnosis of intracranial complications like intracranial bleeding, cerebral herniation and loss of differentiation in grey and white matter (71). MRI axial T2 imaging is better, as compared to CT in demonstrating cerebral oedema at an early stage, due to its ability to give morphological and physiological information at a cellular level (71). In ALF, a cytotoxic rise of intracellular water is the predominant cause (rather than a vasogenic rise in interstitial water) in producing cerebral oedema. MRI sequences such as FLAIR ADC, DWI help differentiate between vasogenic versus cytotoxic cerebral oedema (72). In acute hyperammonemia, the changes are subtle and T2/FLAIR brain MRI may show symmetric high signal within the insula (most common) thalamus and posterior limbs of gyrus often reversible with therapy. There is severe diffuse cortical oedema and hyper intensity and periolandic and occipital regions are typically spared. In SWI MRI sequence, nearly one half have microhemorrhages of white matter or cortex (73). Magnetic resonance spectroscopy (MRS) is helpful in the evaluation of mitochondrial ALF, in the setting of neonatal/infantile ALF. The changes in MRS may be dramatic, but it does not always detect the lactate peak, as it is not always elevated (74); however, CSF lactate is not always easy to measure in ALF patients.

Transcranial Doppler is a non-invasive method of assessing intracranial pressure; however, in a study of children with ALF, neither optic nerve sheath diameter nor transcranial doppler pulsatility index was reliable in the diagnosis of ICP evaluation (75). Transcranial doppler estimating cerebral perfusion with arterial velocities had a negative predictive value for raised intracranial pressure (75).

In the diagnosis of HLH, there is a role for FLAIR and T1 weighed images in MRI, where leptomeningeal and parenchymal involvements are noted. In GALD, the MRI T2 sequence of the abdomen may be useful in detecting pancreatic iron deposition, suggestive of the diagnosis (76). Multidimensional CT (MDCT) dynamic enhancement may detect loss of liver volume in a patient with ALF (ie, after DILI), indicating the need for LT. Future imaging in ALF may include diffusion tensor imaging and functional MRI (fMRI) for imaging the aspects of blood flow and measuring regional variations in brain activity and neurocognitive changes. Near-infrared spectroscopy (NIRS) and functional NIRS may detect cerebral hyperperfusion, before the onset of intracranial hypertension in ALF (77).

In conclusion, neuroimaging should be considered for management decisions in ALF, given that it will not worsen the patient’s condition. MRS should be considered in all children with a high index of suspicion for mitochondrial disorders, and MRI of the abdomen/pancreas should be considered in neonates with a high index of suspicion for GALD.

Intensive Care Management: Lessons Learned From Adults

ALF in adults and ALF in children have common pathophysiological features. An overexpression of monocytes and macrophages frequently results in multiorgan failure. The etiology of ALF in adults differs from children with the leading cause being paracetamol overdose (0–60%) in the Western world, viral hepatitis (5–50%) in Asia, indeterminate (10–40%) and other causes (hypoxic hepatitis due to cardiac failure, hemochromatosis, Wilson’s, AIH, pregnancy-related).

Studies first undertaken and published in adult patients with ALF (ie, use of NAC in non-APAP, advantage of continuous over intermittent forms of renal replacement therapy and its effects on HE and ICP have been replicated in pediatric patients (78–80). RCT’s in small adult series on ALF using phenytoin and liver assist devices have not shown a benefit in mortality rates (81–88). In contrast, therapeutic plasma exchange (TPE) has been shown to improve transplant-free survival with statistically significant impact on mortality (89). Plasma exchange is now also performed in PALF (52). Bedside monitoring, imaging and interventions are often not age dependent. In the intensive care unit (ICU), early point of care US imaging (POCUS), advanced hemodynamic monitoring and organ-based, timely, aggressive resuscitation supported by extracorporeal therapies is performed concomitantly. Great care needs to be taken to prevent therapy-induced organ injury. Concerning the cardiovascular system, we consider imaging is important, and as hemodynamic monitoring with central femoral and axillary arterial access necessary, to avoid peripheral versus central arterial pressure bias. Hemodynamic monitoring is performed in adults with ongoing, not infrequent use of the pulmonary artery catheter and when there are concerns around right or left ventricular function. Under these circumstances, pressure, flow and mixed venous oxygen saturation monitoring are helpful. Functional hemodynamic monitoring via pulse pressure variation (PPV) based on calibrated pulse contour analysis can predict fluid responsiveness under appropriate conditions (80). In a recent controlled trial, only one-third of ALF patients were “fluid responders.” Intravenous fluids are drugs and should be administered with caution and based on physiological targets derived from appropriate monitoring. Tissue oxygenation monitoring via measurement of sublingual blood flow or through infrared spectroscopy can compliment CVS management (80).

The incidence of ICH has decreased in ALF and PALF, which has been attributed to the earlier use of renal replacement therapy (50–52). Intubation and ventilation, adequate analgo-sedation, normalization of electrolytes, empirical administration of antimicrobials, use of hypertonic saline and rarely mannitol, maintenance of temperature <36°C—targeted temperature management
CONCLUDING REMARKS
The single topic Monothematic Conference organized by the ESPGHAN Hepatology committee, was dedicated to the update on management of ALF in children. The aim of the present proceedings report was to summarize the academic presentations therein and to present standard practice diagnosis and management in PALF by experts in the field; however, it also helped to identify gaps in knowledge and to determine differences in the diagnosis and initial management in the ICU setting between pediatric and adult practices. Causes of ALF in children are different than in adults, and yet, a large number of causes remain unidentified. Children require extensive diagnostic investigations, in the setting of a specialized center that can also perform liver transplantsations in the acute setting in order to establish a correct diagnosis among the numerous metabolic and genetic, immune defects hiding under iPALF. Diagnosis is highly age-dependent. Viral sepsis, GALD and metabolic mitochondrial disorders place neonates and infants at high risk for poor outcomes, unless they receive swift medical treatment, correct imaging, adequate ICU care, and timely and justified referral for LT. In PALF, adequate cardiovascular support, brain imaging, an EEG and, and avoidance of correction of coagulopathy in those without bleeding are some of the important initial steps in the ICU setting. Prognosis of HE could be improved with early recognition (although encephalopathy is clinically difficult to assess in small children and scoring scales are not very applicable), prompt intervention with ammonia lowering medications (effectiveness of ammonia scavengers based on pediatric center experience) and optimization of ICU management. Lessons learned from adult patients in the ICU management do not necessarily apply to children. NAC has not proven to be beneficial for non-APAP-PALF and hypertonic saline has not been used in pediatric non-trauma ICH cases routinely. CCRT is indicated for children admitted for acute renal failure, fluid overload, severe electrolyte disorders, persistent acidosis, hyperammonemia and the prevention of ICH, although settings need to be better determined in pediatrics.

Optimizing current ICU practices, including plasma exchange and hemodialysis techniques, in pediatrics, may improve survival (52). In the view of paucity of pediatric data and lack of convincing adult data, extracorporeal liver support system is not advocated routinely in children (51).

REFERENCES
28. Zellos et al JPGN • Volume 74, Number 3, March 2022


