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Source: Lal BB, Sood V, Gupta E, et al. Severe acute hepatitis of unknown etiology presenting as pediatric acute liver failure: analysis of likely etiology, clinical course and outcome. J Clin Exp Hepatol 2023. DOI: 10.1016/j.jceh.2023.05.014

In this single-center study, authors have analyzed the etiologies, clinical course, and in-hospital outcomes of cases of severe acute hepatitis with acute liver failure (ALF) who presented between May and October 2022. A total of 178 children presented with severe acute hepatitis of known/unknown etiology, including 28 presenting as ALF. Eight of them fulfilled the definition of severe acute hepatitis of unknown etiology presenting as ALF. Adenovirus was not associated with cases of ALF in these children. Severe acute respiratory syndrome coronavirus 2 antibodies were detected in six (75%) of them. They have concluded that children with severe acute hepatitis of unknown etiology presenting as ALF were young (median age 4 years), had a hyperacute presentation with a predominance of gastrointestinal symptoms, and a fulminant course with worse outcomes (native liver survival 25%).

Source: Bolia R, Thapar N. Celiac disease in children: a 2023 update. Indian J Pediatr 2023. DOI: 10.1007/s12098-023-04659-w

In this review article, the authors have highlighted that although initial descriptions of celiac disease (CeD) focused on the classical presentation with gastrointestinal manifestations, recently, it has been noted that more patients have nonclassical manifestations such as anemia, osteoporosis, increased transaminases, growth failure, or short stature. Conclusive diagnosis of CeD relied on a combination of clinical history and serologic testing with/without examination of duodenal biopsies. The preferred initial serologic test, regardless of age, for the detection of CeD is the tissue transglutaminase [immunoglobulin A (IgA) anti-tTG]. Children with a high tTG-IgA (≥10 units above the upper limit of normal) and a positive anti-endomysial IgA antibody can be diagnosed with CeD without the need for duodenal biopsies. The rest should undergo biopsies, with at least four biopsies from the distal duodenum and at least one from the bulb. A correctly orientated biopsy showing increased intraepithelial cells and a villous-to-crypt ratio of <2 is suggestive of CeD. The management of CeD is a lifelong, complete dietary avoidance of gluten. IgA-tTG acts as a surrogate marker for healing of the small-bowel mucosa and should be performed every 6 months until normalization and then every 12–24 months subsequently.

Source: Vinayagamoorthy V, Srivastava A, Das I, et al. Hypocoagulability in children with decompensated chronic liver disease and sepsis: assessment by thromboelastography. JPGN Rep 2023;4(3):e324. DOI: 10.1097/PG9.0000000000000324

In this prospective pilot study, the authors have evaluated the coagulation status of children with decompensated chronic liver disease (DCLD) and infection and factors affecting it, using thromboelastography (TEG) in nontransplant settings. Coagulation status of children admitted with DCLD and infection was assessed by the international normalized ratio (INR), platelet count, and TEG [reaction time (R), kinetic time (K), α-angle (AA), maximum amplitude (MA), coagulation index (CI), and lysis index (LY30)] at admission and at 7–14 days after treatment. Among the 30 children enrolled, 29 (96.7%) had a prolonged INR, 24 (80%) had thrombocytopenia, and 17 (56.6%) were hypocoagulable by TEG at admission. Nine of 30 (30%) had normal TEG but deranged INR and platelets. Authors have concluded that 57% of children with DCLD and infection were hypocoagulable by TEG. Severe sepsis and persistent systemic inflammatory response syndrome (SIRS) worsened the coagulation status. TEG identifies bleeders better than INR and platelet count. R-time of ≥8.5 minutes predicted mortality with high sensitivity (83%) and specificity (100%).

Source: Alam S, Lal BB. Pediatric acute-on-chronic liver failure. Indian J Pediatr 2023. DOI: 10.1007/s12098-023-04717-3

In this review article, authors have pointed out that there is a lack of consensus definition for pediatric acute-on-chronic liver failure (ACLF). Wilson disease (WD) and autoimmune hepatitis (AIH) are the most common causes of underlying cirrhosis in children, with acute viral hepatitis and flares of WD and AIH being the most common acute precipitating events. Poor outcomes [death and liver transplantation (LT)] ranging from 19 to 59% have been reported. Prognosis in pediatric ACLF is generally better than that in adults due to a greater proportion of treatable etiologies, lesser organ failures, comorbidities, and better hepatic reserves. The Asia Pacific Association for Study of Liver Diseases ACLF Research

Consortium score of ≥11 is predictive of poor 28–90-day mortality. Bridging therapies, especially high-volume plasma exchange, can be initiated early as a bridge to LT or native liver recovery. Those with no improvement in 4–7 days should undergo LT before the development of sepsis or multi-organ failure.

Source: Bolia R, Srivastava A. Ascites and chronic liver disease in children. Indian J Pediatr 2023. DOI: 10.1007/s12098-023-04596-8

In this review article, authors have emphasized that diagnostic paracentesis should be performed in liver disease patients with-new-onset ascites at the beginning of each hospital admission and when ascitic fluid infection (AFI) is suspected. They have highlighted that ascites have been reported in children with noncirrhotic liver diseases like acute viral hepatitis, acute liver failure, and extrahepatic portal venous obstruction. The routine analysis includes cell count with differential, bacterial culture, ascitic fluid total protein, and albumin. A serum albumin-ascitic fluid albumin gradient of ≥1.1 gm/dL confirms the diagnosis of portal hypertension. AFI (fluid neutrophil count ≥250/mm^3) is an important complication and requires prompt antibiotic therapy. Key steps in the management of cirrhotic ascites include dietary sodium restriction (2 mEq/kg/day (max 90 mEq/day) of sodium/day), diuretics [aldosterone antagonists (e.g., spironolactone) with or without loop-diuretics (e.g., furosemide)] and large-volume paracentesis (LVP). Once the ascites is mobilized, the diuretics should be gradually tapered to the minimum effective dosage. Tense ascites should be managed with an LVP with albumin infusion. Therapeutic options for refractory ascites include recurrent LVP, transjugular intrahepatic portosystemic shunt, and liver transplantation.

Source: Ramaswamy PK, Jana M, Sharma R, et al. Novel scoring systems and age-based hepatic shear wave stiffness cut-offs for improving sonographic diagnosis of biliary atresia. Indian J Pediatr 2023. DOI: 10.1007/s12098-023-04607-8

Authors have aimed to make sonographic evaluation for biliary atresia (BA) more objective and reproducible using scoring systems and evaluate hepatic shear wave elastography (SWE) as an adjunct in sonographic diagnosis of BA in this prospective observational cohort study 64 infants with cholestatic jaundice were enrolled between June 2016 and March 2018. Sonography and SWE were performed with the SuperSonic Aixplorer system. Novel scoring systems were developed incorporating established sonographic parameters and hepatic stiffness values and analyzed using Statistical Package for the Social Sciences software. Of the 18 patients confirmed as BA, three were misdiagnosed on conventional sonography (16.7%) as non-BA. Gallbladder (GB) wall irregularity and fasting GB length were the most accurate (93.8%) and most specific (97.8%) individual parameters, respectively. A significant difference was noted in the triangular cord (TC) thickness of BA and non-BA infants ($p < 0.001$), with a high specificity of 95.6% for a 4 mm cut-off value for a positive TC sign. Comparison of hepatic SWE stiffness among age-matched groups of BA and non-BA showed significant differences (≤60 days: $p = 0.003$; >60 days: $p < 0.001$) but with a reduced accuracy (93.8%). Diagnostic accuracy of the grayscale scoring system (96.9%), grayscale + elastography scoring system in ≤60 days (94.4%) and >60 days (97.8%) were better than that of conventional sonographic diagnosis (93.8%). They have concluded that the grayscale scoring system improves the accuracy of sonographic diagnosis of BA without any additional cost or time penalty.

Source: Seetharaman J, Srivastava A, Yadav RR, et al. Visceral fat indices: do they help differentiate Crohn's disease and Intestinal tuberculosis in children? J Crohn's Colitis 2023;jjad109. DOI: 10.1093/ecco-jcc/jjad109

In this single-center study, authors have evaluated the utility of fat indices [visceral fat (VF) and subcutaneous fat (SF)] in differentiating Crohn's disease (CD) and intestinal tuberculosis (ITB) in children. Abdominal fat was measured on computed tomography in a supine position at the level of L4 vertebrae. VF and SF area were measured separately by a radiologist, blinded to the diagnosis. Sum of VF and SF was taken as total fat (TF). VF/SF and VF/TF ratios were calculated. A total of 34 [age 14 (10.8–17.0) years, 14 boys] children were enrolled. Only 12 had CD [seven boys, age 13.0 years], and 22 had ITB [seven boys, age 14.5 years]. VF area was higher in CD compared to ITB. A VF:SF ratio of 0.609 predicted CD with good sensitivity (75%) and specificity (86.4%) (area under the curve, 0.795; 95% confidence interval 0.636–0.955; $p = 0.005$), particularly in boys. Authors have concluded that the VF/SF ratio is a simple, noninvasive, objective parameter to differentiate CD and ITB in children, particularly boys.

Source: Lal R, Bhardwaj R, Minz RW, et al. Usefulness of a double immunofluorescence technique for detection of intestinal tTG-IgA deposits in diabetic and non-diabetic children with celiac disease. Pediatr Neonatol 2023; 64(4):388–397. DOI: 10.1016/j.pedneo.2022.01.012

This single-center study authored has tested the usefulness of the double staining immunofluorescence (dsIF) technique for the detection of intestinal anti-tissue transglutaminase specific immunoglobulin A (IgA) antibody (tTG-IgA) deposits in celiac disease (CeD) and type 1 diabetes mellitus (T1D) children with coexisting CeD. A total of 46 patients (30 cases of CeD and 16 cases of T1D with CeD) and 16 nondiabetic, nonceliac children were enrolled. Endoscopic biopsies were taken and analyzed by light microscopy, quantitative histology (QH), and a dsIF technique. Histologically, villous atrophy was most severe in CeD, followed by T1D with CeD, while all control biopsies except one were normal. QH showed a statistically significant difference in villous height (Vh), crypt depth (CrD), and Vh:CrD ratio between diabetic and nondiabetic patients with CD. dsIF technique could detect tTG-IgA deposits in 85.7% of cases of CD alone and 93.8% of biopsies from diabetic children. Deposits were more extensive in biopsies with minimal villous shortening, and five biopsies from T1D patients with normal histology were dsIF positive. Authors have concluded that *in situ* analysis of tTG-IgA immune deposits facilitates the detection of positive serology early-onset CeD.

Source: Poddar U, Samanta A, Sarma MS, et al. How to suspect the presence of high-risk esophageal varices and when to start endoscopic surveillance in children with biliary atresia? J Gastroenterol Hepatol 2023. DOI: 10.1111/jgh.16267

In this cohort study, authors have evaluated the utility of noninvasive tests [splenomegaly (clinical and USG), platelet count, aspartate transaminase to platelet ratio index (APRI), and platelet-to-spleen diameter ratio] in detecting high-risk esophageal varices (grade II with red-color signs or grade III or IV irrespective of red-color signs) in biliary atresia (BA). In their cohort of 110 children {75 boys [66 successful Kasai Procedure (KPE) and 44 failed/KPE not performed]}, the first endoscopy revealed gastroesophageal varices in 75.4% of cases, and 32% of them had high-risk varices. Multivariate analysis revealed failed KPE, history of upper gastrointestinal bleeding, bigger spleen size (>3.5 cm), lower platelet count (<150,000), and higher APRI (>2) are independent predictors of the presence of high-risk esophageal varices. They

have concluded that early surveillance endoscopy should be done in children with BA who have splenomegaly, thrombocytopenia, and high APRI scores to prevent variceal bleeding.

Source: Vadlapudi SS, Srivastava A, Rai P, et al. Jaundice in a child with sickle cell anemia: a case based approach. Indian J Pediatr 2023. DOI: 10.1007/s12098-023-04747-x

Through this illustrative case report, authors have presented a child with sickle cell anemia (SCA) and conjugated hyperbilirubinemia due to biliary obstruction. He underwent endoscopic retrograde cholangiopancreatography and biliary stenting, had complications of postsphincterotomy bleed, retroperitoneal hematoma, and postlaparoscopic cholecystectomy sepsis with an acute sickle hepatic crisis which was managed successfully. Authors have presented a stepwise approach in the management of sickle cell hepatopathy and emphasize that patients with SCA and conjugated hyperbilirubinemia carry "high risk" and are best managed by a multidisciplinary team.

Source: Deniz S, Schinner R, Monroe EJ, et al. Outcome of children with transjugular intrahepatic portosystemic shunt: a meta-analysis of individual patient data. Cardiovasc Intervent Radiol 2023. DOI: 10.1007/s00270-023-03520-z

In this meta-analysis, authors have aimed to investigate outcomes after pediatric transjugular intrahepatic portosystemic shunt (TIPS) with respect to survival by extracting patient data retrieved from five retrospective cohorts from different parts of the world. There was heterogeneity in the indication for TIPS among 135 children enrolled in this study. They have concluded that the presence of ascites was associated with impaired survival (hazard ratio 2.3, $p = 0.023$) after TIPS in children, with no differences in survival according to the age of the child, emphasizing the feasibility of interventional shunt procedure across all ages.

Source: Srivastava A, Poddar U, Mathias A, et al. Achalasia cardia sub-types in children: Does it affect the response to therapy? Indian J Gastroenterol 2023;42(4):534–541. DOI: 10.1007/s12664-023-01344-w

In this single-center study, authors have aimed to investigate the differences in clinico-laboratory features and response to therapy between achalasia subtypes in children. A total of 48 children were enrolled in the study. All children diagnosed with achalasia underwent clinical, barium, high-resolution manometry (HRM), gastroscopy, and sub-type, which was determined by Chicago Classification at HRM. Pneumatic dilatation (PD) or surgery was the primary therapy. Success was defined as Eckhardt's score of ≤3. A timed barium esophagogram (TBE) was used for assessing therapeutic response. Adequate HRM study could be done in 40 cases: type I (*n*—19), II (*n*—19), and III (*n*—2). The most common symptoms were dysphagia and regurgitation. Type II achalasia had higher lower esophageal sphincter pressure and less dilated esophagus than type I. They have concluded that both types I and II achalasia shared a similar clinical profile and responded well to initial PD, but type I achalasia required post-PD myotomy more than type II achalasia.

Missed in Earlier Issues

Happy Tummy Consortium, Lavalle L, Sauvageot N, et al. Infant feeding practice and gastrointestinal tolerance: a real-world, multi-country, cross-sectional observational study. BMC Pediatr 2022; 22(1):714. DOI: 10.1186/s12887-022-03763-8

The primary objective of this observational study was to examine gastrointestinal (GI) tolerance in formula-fed infants (FFI) vs breastfed infants (BFI) in a real-world setting, with a secondary objective being the comparison of infants fed formula with pre and/or probiotics (FFI_PP) and those fed formula without any pre and/or probiotics (FFI_noPP) as well as BFI. A six-country, cross-sectional study in full-term exclusively/predominantly FFI ($n = 2036$) and BFI ($n = 760$) aged 6–16 weeks was conducted using the validated Infant Gastrointestinal Symptom Questionnaire (IGSQ) and a Feeding Practice and Gut Comfort Questionnaire. The IGSQ composite score in FFI was noninferior compared to BFI {mean difference [95% confidence interval (CI)]: 0.17 (−0.34, 0.67); noninferiority p-value <0.0001}, and scores for BFI and FFI were below the threshold of 23, indicating no GI discomfort. Adjusted mean IGSQ scores ± standard error were similar in FFI_PP (22.1 ± 0.2) and BFI (22.3 ± 0.3), while FFI_noPP (23.4 ± 0.3) was significantly higher and above 23 indicating some GI discomfort (mean differences [95% CI] FFI_noPP − FFI_PP and FFI_noPP − BFI were 1.28 [0.57, 1.98] and 1.09 [0.38, 1.80], respectively; both $p < 0.01$). Hard stools and difficulty in passing stool were more common in FFI compared to BFI ($p < 0.01$) but were less common in FFI_PP compared to FFI_noPP ($p < 0.01$). FFI_PP showed significantly less crying than FFI_noPP and was similar to BFI. Authors have concluded that FFI had noninferior overall GI tolerance compared to BFI. Within FFI, infants receiving formulas with pre and/or probiotics had a better GI tolerance, improved stooling, and less infantile colic compared to those receiving formula without any pre and/or probiotics and were more similar to BFI.

Source: Lal SB, Venkatesh V, Aneja A, et al. Clinical spectrum & changing presentation of celiac disease in Indian children. Indian J Med Res 2023;158(1):75–84. DOI: 10.4103/ijmr.ijmr_1102_21

In this single-center study from North India, the authors have aimed to assess the clinical, serological, and histological profile of celiac disease (CeD) in a large cohort of children and the changing trends in its presentation. Clinical data of 891 children diagnosed with CeD between 2000 and 2019 regarding demography, symptoms, associated conditions, serology, biopsy findings, and gluten-free diet were analyzed. They have observed that the mean age (±standard deviation) of children at onset and at diagnosis was 4.0 ± 2.7 and 6.2 ± 3.1 years, respectively. Growth faltering, abdominal pain, abdominal distension, and diarrhea were presenting symptoms in 70, 64.2, 61.2, and 58.2%, respectively. Family history of CeD was present in 14% and autoimmune conditions in 12.3% of children. Thyroid disorders were seen in 8.5% of children, and type 1 diabetes mellitus in 5.7%. The duration of breastfeeding had a weak positive correlation with age at onset and diagnosis of CeD ($p < 0.001$). Nonclassical CeD was significantly more common in children aged >10 years and in those presenting after 2010 ($p < 0.01$). Authors have concluded that infants and young children were more likely to present with classic symptoms of diarrhea, abdominal distension, and growth failure, while older children presented with nonclassical CeD.There was a trend toward nonclassical forms of CeD in recent years.

Source: Kesavelu D, Jog P. Current understanding of antibiotic-associated dysbiosis and approaches for its management. TherAdv Infect Dis 2023;10:20499361231154443. DOI: 10.1177/20499361231154443

Antibiotic-associated diarrhea (AAD), *Clostridiodes difficile*-associated diarrhea (CDAD), and *Helicobacter pylori* infection are all short-term consequences of antibiotic treatment that persist from a few weeks to months. Changes in gut microbiota, which persist even 2 years after antibiotic exposure, and the development of obesity,

allergies, and asthma are among the long-term consequences. Probiotic bacteria and dietary supplements can potentially prevent or reverse antibiotic-associated gut microbiota dysbiosis. Probiotics have been demonstrated in clinical studies to help prevent AAD and, to a lesser extent, CDAD, as well as to improve *Helicobacter pylori* eradication rates. In the Indian setting, probiotics (*Saccharomyces boulardii* and *Bacillus clausii*) have been shown to reduce the duration and frequency of acute diarrhea in children. Antibiotics may exaggerate the consequences of gut microbiota dysbiosis in vulnerable populations already affected by the condition.

Source: Seetharaman K, Lal SB, Prasad KK, et al. Role of serology, dietary assessment, and fecal gluten immunogenic peptides for predicting histologic recovery in children with celiac disease. Dig Dis Sci 2023;68(2):529–540. DOI: 10.1007/s10620-022-07762-8

In this single-center, prospective observational study, authors have compared the ability of various modalities used to assess compliance to a gluten-free diet (GFD) for predicting persistent mucosal damage in children with celiac disease. A total of 153 children (mean age 12.2 ± 3.6 years, 58% boys) on GFD (mean duration 6 ± 3.1 years) were recruited. Persistent mucosal damage was seen in 88% of the enrolled. Fecal gluten immunogenic peptide (GIP) was positive in 87.8% (129/147). Antibodies to tissue transglutaminase [TGA-immunoglobulin A (IgA)] and/or deamidated gliadin peptide were positive in 32% (48/150) whereas antibody to synthetic neoepitopes of TGA-IgA was positive in 24.8% (37/149). Noncompliance, as assessed by the local questionnaire, Biagi score, and dietitian detailed interview, were 62.7, 60, and 75.3%, respectively. Serology had the highest specificity (83%) and fecal GIP had the highest sensitivity (89%). On logistic regression analysis, only noncompliance with the Biagi score predicted poor mucosal recovery. Authors have concluded that none of the existing modalities used to assess compliance to GFD accurately predict persistent mucosal damage. Fecal GIP may be sensitive to detect only "one-point dietary transgression."