**STUDY 1:**

**LUMINAL GASTROENTEROLOGY:**

*Bittker SS, Bell KR. Potential risk factors for celiac disease in childhood: a case-control epidemiological survey. Clin Exp Gastroenterol. 2019;12:303–319. Published 2019 Jul 4. doi:10.2147/CEG.S210060*

Incidence of ear infection before 2 years old, courses of antibiotics before 2 years, duration of breastfeeding, vitamin D drop exposure in infancy, vitamin D supplement exposure between 2–3 years old, age at gluten introduction into the diet, fat content of cow's milk consumed between 2–3 years old, quantity of cow's milk consumed between 2–3 years , and type of water consumed at 2 years old were the nine variables studied in this retrospective survey. Questionnaire responses were collected from 332 children/parents with Celiac disease and 241 who do not have Celiac disease. Differential recall bias was the potential inbuilt bias in this study.

The data suggested that consumption of skim milk as the primary form of liquid cow's milk between 2-3 years old was associated with celiac disease. (Adjusted odds ratio [aOR]=3.556, CI=1.430–10.22, P=0.010). Infants who receive oral vitamin D drops for longer than 3 months were at increased risk of celiac disease later in life. (aOR=1.749, CI=1.079–2.872, P=0.025).

Courses of antibiotics (aOR=1.133, CI=1.037–1.244, P=0.007), and incidence of ear infection (aOR=1.183, CI=1.041–1.348, P=0.010) were all associated with celiac disease. It was prospective in nature.

Skim milk and Vitamin D supplementation association with celiac disease were interesting findings. Scientific basis of the same in literature was well presented in discussion. Prospective studies are needed to validate the findings.

**STUDY 2:**

**LUMINAL GASTROENTEROLOGY :**

*The Use of Jejunal Tube Feeding in Children: A Position Paper by the Gastroenterology and Nutrition Committees ofthe European Society for Paediatric Gastroentrology, Hepatology, and Nutrition 2019. J Pediatr Gastroenterol Nutr. 2019 Aug;69(2):239-258. DOI:10.1097/MPG.0000000000002379*

Jejunal tube feeding (JTF) is defined as postpyloric feedingthrough a feeding tube with its tip placed at least 40 cm distally to ligament of Treitz.

ESPGHAN expert group recommends jejunal feeding as the route of choice for providing enteral nutrition (EN) in children with failure of oral and intragastric feeds or gastric outlet obstruction. It is also suggested in children with pediatric intestinal pseudo-obstruction who fail gastrostomy feeding. Group recommends considering JTF as an alternative to fundoplication and gastrostomy tube feeding in children with severe gastroesophageal reflux with risk of aspiration. In children with acute pancreatitis Jejunal tube feeding is recommended only in cases in which oral or gastric feeding is not tolerated.

Group recommends a trial of continuous gastric feeding with a hydrolysed or elemental formula before postpyloric feeding is started. Group recommends considering trial of at least 1 prokinetic drug to promote oral or gastric feeding before instituting jejunal feeding.

Contrast meal and follow through study of the small intestine in all patients to ensure patency of the intestinal lumen and exclude a mechanical obstruction before jejunal feeding tube placement is suggested. Upper GI endoscopy is must in all patients before JTF placement.

Paralytic or mechanical ileus,intestinal obstruction, intestinal perforation, peritonitis,

and necrotizing enterocolitis are absolute contraindications. Group recommends not using JTF in preterm infants. Standard polymeric formula can be used if it is not tolerated switch to a hydrolysed formula. Avoid use of JTF for the administration of medication. Deliveries of medication via the jejunal route have unpredictable bioavailability of the active component, the absorption site of the drug, potential local adverse effects, and potential reaction with the feeding tube.

**STUDY 3:**

**HEPATOLOGY:**

*Shalby, M. M., Ibrahim, S. A., Behairy, O. G., Behiry, E. G. and Mahmoud, D. A. (2019), Diagnostic value of serum cytokeratin-18 in children with chronic liver disease. J Paediatr Child Health. doi:10.1111/jpc.14488*

Liver biopsy is the gold standard for diagnosis in chronic hepatitis and liver disease. The main aim of the study was to assess the diagnostic value of serum cytokeratin-18 (CK-18) in children with chronic liver diseases (CLD) and to correlate with liver histology.

In this study Serum concentrations of CK-18 were measured using human enzyme-linked immunosorbent assay (sandwich technique) kits. Only apoptotic factor in children with CLD was studied. Liver biopsy was performed for all cases. Severity of liver disease was evaluated according to the Child-Pugh score, model for end-stage liver disease (MELD) for older than 12 and child-related end-stage liver disease (PELD) score for participants younger than 12 years of age.

Study shows that the serum concentrations of CK- 18 were significantly elevated in CLD patients than healthy controls (1070.63 +/- 699.2 ng/mL). There was a positive correlation between CK-18 levels and total IgG, pediatric end-stage liver disease score and model for end-stage liver disease scores. The best cutoff point of CK-18 was 624 ng/mL, sensitivity 93.06%, specificity 62.5% and diagnostic accuracy 90.0% for detection of fibrosis. Multiple linear regression analysis indicated that CK18, AST,PELD, platelet and WBC were important variables detecting fibrosis in children. Small sample size, 80 was the limitation factor in the study.

Comments: Cytokeratin 18(CK18) is an intermediate filament protein highly expressed in epithelial cells. When released into extracellular space, CK18 can be used as biomarker. Apoptosis and necrosis are the two major approaches to hepatocyte cellular death. Caspase cleaved keratin 18 (CCK18) is considered to represent hepatocyte apoptosis measured by M30 antibody ELISA. Keratin 18 (cleaved & un-cleaved) represents necrosis measured by M65 ELISA antibody. M30: M65 ratio is proposed to differentiate apoptotic and necrotic cell death in various studies. M65 levels are higher in ALF (Acute liver failure) as compared to ACLF (Acute on chronic liver failure) in the literature. The limitation of this biomarker is the presence of cytokeratin in non hepatic epithelium. Extra hepatic epitheliolysis can also raise the biomarker levels. In clinical settings, combined and mixed pattern of injury and association with sepsis make it a complex scenario. It does make health of liver and manner of predominant hepatocyte death difficult to analyze. Never the less it underscores importance of newer Liver function test at molecular level. These biomarkers in pediatric liver disease require further validation.

**STUDY 4:**

**HEPATOLOGY :**

*Chapin, C.A., Burn, T., Meijome, T., Loomes, K.M., Melin-Aldana, H., Kreiger, P.A. et al. Indeterminate pediatric acute liver failure is uniquely characterized by a CD103+CD8+ T-cell infiltrate. Hepatology. 2018; 68: 1087–1100 DOI:10.1002/hep.29901*

This was a retrospective and prospective study of PALF; pediatric acute liver failure cases due to indeterminate (iPALF), autoimmune hepatitis

(AIH), or known diagnosis (dPALF) etiology. Liver tissue sections were stained with immunohistochemical (IHC) markers for cytotoxic T-cells (CD8), perforin, and tissue resident memory T-cells (CD103), and scoredas minimal, moderate, or dense. Lymphocytes were isolated from liver tissue for T-cell receptor beta (TCRβ) sequencing and flow cytometry studies.

iPALF cases were characterized by dense CD8+ T-cell hepatic infiltrate. It represents immune dysregulation. This was the first study to demonstrate that histopathologic feature, specifically CD8 staining, differentiates iPALF (indeterminate) from dPALF (diagnosed). Macrophage density was also significantly increased in iPALF compared to AIH (Autoimmune Hepatitis) and dPALF cases. The degree of hepatocyte necrosis was associated with macrophage activity. CD8 T-cell phenotype cells were perforin positive in Indertminate liver failure group. The majority of cases showed minimal perforin staining in d PALF group. CD8+ T-cells of iPALF were largely positive for the Trm marker CD103, which was not seen among the dPALF.

CD 8 positive immune dysregulation was associated with bone marrow suppression in associated cases of aplastic anaemia in the series. iPALF patients in the study who developed aplastic anaemia had on peripheral blood flow cytometry decreased CD4:CD8 ratio (due to an increase in CD8 cells). This study also proposes low CD4:CD8 ratio as an additional biomarker of the iPALF immunedysregulation. CD8 staining density was still significantly increased in the iPALF compared to the AIH group. Both had different phenotypes.

Indeterminate acute liver failure seems to have a different immune-pathophysiology. Molecular biomarkers in liver biopsy and in peripheral smear would further help us in understanding and developing newer approaches for treatment.

**STUDY 5:**
**HEPATOLOGY :**

*Chapin, Catherine A. et al.Corticosteroid Therapy for Indeterminate Pediatric Acute Liver Failure and Aplastic Anemia with Acute Hepatitis The Journal of Pediatrics, Volume 208, 23 – 29 DOI:10.1016/j.jpeds.2018.12.042*

This was a multicenter patient cohort study with indeterminate pediatric acute liver failure (I-PALF) and aplastic anemia. The patients were treated with corticosteroids. It was a retrospective study. Aplastic anemia with acute hepatitis was defined as (1) no known evidence of chronic liver disease; (2) biochemical evidence of acute liver injury with onset of illness within 8 weeks of presentation and alanine aminotransferase (ALT)≥500; and (3) aplastic anemia based on peripheral blood cytopenias and hypocellular bone marrow biopsy. Cases were defined as indeterminate if no known cause for their liver disease was identified despite an age-appropriate diagnostic evaluation.

0.5-4 mg/kg/day of intravenous methylprednisolone, was used in most cases. 8 patients received bolus doses of 10 mg/kg/day for several days followed by a taper. By 21 days, postcorticosteroid initiation, 50% required liver transplantation, 46% recovered with their native liver, and 4% died. Patients who recovered with their native liver received a median of 139 days (range 19-749) of corticosteroid therapy.

Patients with aplastic anemia with acute hepatitis (n = 6), received 1-2 mg/kg/day of methylprednisolone for a median of 100 days (range 63-183), and all recovered with their native liver.

Empiric use of corticosteroids was suggested in I-PALF with the strongest evidence of an immune dysregulation phenotype including evidence of T-cell activation such as elevated sIL-2R levels, and liver biopsy with predominant CD8+ T-cell inflammation. A randomized controlled trial exploring the benefits and risks of steroid therapy is needed.

**Compiled by: Dr. Yogesh Waikar**