**Hepatology Update: Neonatal Cholestasis Syndrome**

**STUDY 1:** Yang, L. , Zhou, Y. , Xu, P. , Mourya, R. , Lei, H. , Cao, G. , Xiong, X. , Xu, H. , Duan, X. , Wang, N. , Fei, L. , Chang, X. , Zhang, X. , Jiang, M. , Bezerra, J. A. and Tang, S. (2018), Diagnostic Accuracy of Serum Matrix Metalloproteinase-7 for Biliary Atresia. Hepatology, 68:2069-2077. doi:10.1002/hep.30234

Early diagnosis and treatment is required to improve clinical outcome in neonatal cholestasis syndrome. Neonatal Hepatopathy and Cholangiopathy are predominantly considered in this spectrum. Recent advances in this field are making the algorithmic approach more decisive. Serum matrix metalloproteinase-7 (MMP-7) is suggested to have discriminatory features for infants with Biliary Atresia. MMP-7, a protease involved in intercellular signaling through breakdown of extracellular matrix. The study concludes that serum MMP-7 assay has high sensitivity and specificity to differentiate Biliary Atresia from other neonatal cholestasis. The area under the curve of MMP-7 for the diagnosis of Biliary Atresia(BA) was 0.9900 with a cutoff value of 52.85 ng/mL; the diagnostic sensitivity and specificity are 98.67% and 95.00%, respectively, with a negative predictive value of 98.28%.

The diagnosis of BA was made by the presence of fibrosing obstruction of extrahepatic biliary remnants excised after intraoperative cholangiography. The authors studied MMP-7 among healthy controls (n=72 with 54 <6 months) and among 135 with cholestasis (75 with BA, 60 with non-BA). Median concentration for MMP-7 was 2.86 ng/mL in healthy controls, 11.47 ng/mL for non-BA cholestasis, and 121.1 ng/mL for BA. The predictive value for MMP-7 was particularly impressive, 74 of 75 BA subjects were correctly identified as having BA. Only 3 non-BA patients were incorrectly assigned a BA diagnosis based on MMP-7 values. Study also compares GGT with MMP-7 which showed a superior performance for MMP-7.Further studies with larger sample size are needed. One of the limitations includes insufficient data for the differentiating with MMP7 other rare cholestatic liver diseases such as Alagille syndrome, alpha-1-antitrypsin deficiency, citrin deficiency, and ductal plate malformation.

**STUDY 2:** Large-scale proteomics identifies MMP-7 as a sentinel of epithelial injury and of biliary atresia *Science Translational Medicine* 22 Nov 2017:Vol. 9, Issue 417, eaan8462 DOI: 10.1126/scitranslmed.aan8462

Using large-scale proteomics, the authors screened 1129 proteins in a cohort (n=70) of patients with BA. They identified several proteins that are increased with BA. Slow off-rate modified aptamer scan (SOMAscan, SomaLogic Inc.) applied to 70 serum samples from a cohort of infants at the time of diagnosis of BA (at Kasai operation, $n = 35$) and to age-matched infants with neonatal intrahepatic cholestasis (IHC; $n = 35$)

Matrix metalloproteinase-7 (MMP-7) is the lead biomarker. MMP-7 is constitutively expressed by normal cholangiocytes, increases in the serum upon biliary injury, and modulates the clinical phenotype in an experimental model of BA as concluded in the study.

MMP-7 is more accurate than gamma glutamyltranspeptidase (GGT). The combination of MMP-7 and GGT has a AUROC of 0.94 in validation cohorts. The authors further studied the role of MMP-7 by immunostaining and found it primarily was detected in cholangiocytes of intrahepatic bile ducts in infants with BA. MMP-7 expression in the liver do not correlate with fibrosis. Immunostaining showed minimal or no expression of MMP-7 in parenchymal or nonparenchymal cells of the normal liver. In liver biopsies obtained at the

time of diagnosis of BA, MMP-7 is detected in cholangiocytes of intrahepatic bile ducts (IHBDs). Livers from BA subjects had higher *MMP-7* mRNA expression compared to Intra Hepatic Cholestasis (fold change relative to normal controls, 9.98 ± 7.65 versus 2.54 ± 1.73; $P < 0.0001$) The data defined a primary localization of MMP-7 in cholangiocytes of extrahepatic bile ducts ( EHBDs), with minimal or no expression in intrahepatic cholangiocytes of normal livers and detectable expression in intrahepatic cholangiocytes of diseased livers (but lower than the level seen in EHBDs).

**Luminal Gastroenterology Update: GERD. (Gastroesophageal Reflux Disease)**

**STUDY 1:** Mechanisms of Aerodigestive Symptoms in Infants with Varying Acid Reflux Index Determined by Esophageal Manometry .Collins, Carissa R. et al. The Journal of Pediatrics, March 2019 Volume 206, 240 – 247 https://doi.org/10.1016/j.jpeds.2018.10.051

The study interprets that symptoms alone are not able to predict the degree or presence of reflux in infants. Symptomatic neonates (n = 74) born at a median of 28.9 weeks gestation using 24-hour pH-impedance to determine (Acid reflux index) ARI severity, followed by provocative esophageal manometry with graded mid esophageal infusions (0.1-5.0 mL) of air, water, and apple juice is done. The effects of 2635 separate esophageal stimuli on reflexes and symptoms are analyzed. The authors considered ARI <3% as normal, 3-7% as indeterminate ARI, and >7% as abnormal ARI. Nonacid reflux is much more likely to provoke symptoms in this population than acid reflux, further questioning blind use of proton pump inhibitors and acid suppressor. Symptoms recorded are arching, irritability, cough, gag, sneeze, gasp, bradycardia, desaturation, throat clearing, startle, grimace, grunting, mouthing, and yawning. GERD severity plays no role in the generation of symptoms. The study concludes that symptoms and peristaltic reflexes are manifestations of the recruitment of several neurosensory and neuromotor pathways evoked by mid-esophageal infusions. ARI severity grade plays no role in symptom generation. GERD should not be diagnosed and severity should not be assigned based on symptoms alone.

**STUDY 2:** Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. (JPGN 2018;66: 516 –554) doi:10.1097/MPG.0000000000018 89

The published guidelines reinforce important clinical points to be followed in the practice. Few of the important recommendations are highlighted here. The working group suggests not using barium contrast studies for the diagnosis of GERD in infants and children. Based on expert opinion, the working group suggests to use esophago-gastro- duodenoscopy with biopsies to assess complications of GERD, in case an underlying mucosal disease is suspected, or prior to escalation of therapy. The working group suggests scintigraphy should not be used for the diagnosis of GERD in infants and children. They recommends not to use positional therapy (ie, head elevation, lateral and prone positioning) to treat symptoms of GERD in sleeping infants. The guideline suggests not to use a trial of PPIs as a diagnostic test for GERD in infant while a 4 to 8 week trial of PPIs for typical symptoms (heartburn, retrosternal or epigastric pain) in children as a diagnostic test for GERD can be used. They recommend not using antacids/alginates for chronic treatment of infants and children with GERD. It is advised to avoid use of H2RA or PPI for the treatment of crying/distress in otherwise healthy infants. Based on expert opinion, the working group recommends the use of PPIs as first-line treatment of reflux-related erosive esophagitis in infants and children with GERD.

**STUDY3:** Eichenwald EC and AAP committee on fetus and newborn. Diagnosis and

Management of Gastroesophageal Reflux in Preterm Infants. Pediatrics. 2018;142(1):e2018 1061 DOI: 10.1542/peds. 2018-1061

Highlights of the guidelines are as follows. GER is a normal developmental phenomenon that will resolve with maturation. Signs commonly ascribed to GER in preterm infants include feeding intolerance or aversion, poor weight gain, frequent regurgitation, apnea, and desaturation bradycardia and behavioral signs, including irritability and perceived postprandial discomfort. These signs will usually improve with time without treatment. There is poor data on worsening lung disease attributable to GER and micro aspiration in mechanically ventilated preterm infants. Left lateral body position, head elevation, and feeding regimen manipulation, have not been shown to reduce clinically assessed signs of GER in the preterm infant. Supine positioning on a flat and firm surface and avoidance of commercial devices designed to maintain head elevation in the crib, should be paramount importance in practice. Drugs should be used sparingly, if at all, in preterm infants.

**Luminal Gastroenterology Update: Potential celiac disease.**

**STUDY 1:** Progression of Celiac Disease in Children With Antibodies Against Tissue Transglutaminase and Normal Duodenal Architecture Auricchio, R. et al. Gastroenterology, article in press DOI: https://doi.org/10.1053/j. gastro.2019.04.004

Potential celiac disease is characterized by positive results from serologic tests for tissue transglutaminase antibodies (anti-TG2) but normal duodenal architecture (Marsh stages 0–1). Which patients would progress to overt celiac and which would need observation is a matter of debate. This study highlights on this issue much pending issue.

This is a prospective study of 280 children (ages 2–18 years) in Italy with suspected celiac disease. Enrolled patients have 2 consecutive positive results from tests for anti-TG2, tested positive for the endomysial antibody (anti-EMA), have total serum levels of IgA in the normal range, normal duodenal architecture (Marsh stages 0–1) in 5 biopsies, and HLA DQ2- or DQ8-positive haplotypes. Follow up period is 12 years (range, 18–150 months; median 60 months). Serologic tests and clinical analyses are done in the study every 6 months and a small bowel biopsy was taken every 2 years. A multivariate analysis of clinical, genetic, and histologic data to identify factors associated with progression to villous atrophy is done. The study has a largest cohort of potential celiac disease patients with the longest follow up. Immunohistochemical staining of duodenal biopsy for CD3+, TCRγδ+, and CD25+cells and presence of extracellular deposits of anti-TG2 IgA is done.

42 of 280 children (15%) developed villous atrophy. 89 children (32%) no longer tested positive for anti-TG2 or anti-EMA on follow up. The cumulative incidence of progression to villous atrophy is 43% at 12 years on gluten consumption. Data suggest that prescribing indistinctly to all potential celiac disease patients a GFD (Gluten free diet) would be an overtreatment. Younger patient at diagnosis has a greater chance to remain "potential". Factors most strongly associated with development of villous atrophy are numbers of γδ intraepithelial lymphocyte cells followed by age and homozygosity for the HLA DQB1*02. Lower numbers of γδ positive cells in the intestinal epithelium have been noted to be protective. Marsh 0 lesions at diagnosis on histopathology have less progression to villous atrophy. HLA effect is age specific and is not generalized and needs further research.

**Compiled by :** Dr. Yogesh Waikar
MBBS, MD, DNB,
Fellow in Pediatric Gastroenterology & Liver Transplant
Pediatric Gastroenterologist & Hepatologist.
Super speciality GI Kids Clinics.
Dhantoli, Nagpur, Maharashtra.India.
Email : pedgihep@yahoo.com