JOURNAL WATCH

1. Medical Management of Chronic Pancreatitis in Children: A Position Paper by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Pancreas Committee

Freeman AJ, Maqbool A, Bellin MD et al.Medical Management of Chronic Pancreatitis in Children: A Position Paper by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Pancreas Committee. J Pediatr Gastroenterol Nutr. 2021 Feb 1;72(2):324-340. doi: 10.1097/MPG.0000000000003001.

Chronic pancreatitis (CP) results in overall impairment of quality of life in children. It requires attention in the field of nutrition, pain management, different lifestyle modifications and regular monitoring for the sequela of the disease. North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) Pancreas Committee, presents the first recommendations dedicated to the medical care of children with CP. Endocrine and exocrine insufficiency (EPI) due to CP may lead to delayed puberty and comorbidities associated with malnutrition. To combat the effects a balanced and healthy diet comprising of 45% to 60% carbohydrate, 10% to 30% protein, and 25% to 35% fat is essential along with fat-soluble vitamins A, D, E, and K. Children with CP should be regularly monitored for EPI, growth and pubertal development. This guideline recommends the use of pancreatic enzyme replacement therapy (PERT) in children with proven EPI. PERT can be weight based where the child on oral feeding can be started on 500 to 100 lipase units /kg/ meal with a maximum dose of 3000 lipase units/ kg/meal; it can also be given as 500 to 4000 lipase units/ g of fat intake in children who are on oral feeding or enteral feeding. For children on enteral feeding PERT can be given based on the volume of feed as one prefilled enzyme cartridge for the first 500ml formula and second up to 1000 ml formula. Though there is sparse data of pancreatogenic diabetes mellitus (type 3c DM) in children, the published series mention the prevalence to be 4-9%. Children with CP should be screened yearly for DM with fasting glucose and hemoglobin A1c (HbA1c) level. Oral Glucose tolerance test may be considered if these two parameters are abnormal and should be done annually in pre-diabetics. Anti-oxidants, e.g. Vitamin A, Vitamin C, Vitamin E, selenium, zinc, and methionine, are believed to counter the oxidative stress and depletion of antioxidants due to the fibro-inflammatory effects of CP. But so far there is insufficient data for its use in children with CP. The mechanism pain in CP is poorly understood. It can arise due to pancreatic or extra pancreatic causes or it may be a result of sensitization and increased excitability of pancreatic nociceptors. The multi-modality approach to pain includes a psycho-educational approach with educating parents about coping strategies in the form of cognitive behavioural therapy; physical therapy which can provide a safe and structured environment to start functioning again; use of analgesic ladder incorporating non opioid and opioid drugs; neuro modulators and in extreme cases celiac plexus block. Lifestyle modifications should include a check on the weight with healthy diet and exercise. Development of sequala of CP as pancreatic fluid collections, ductal disease, vascular complications as splenic vein thrombosis, and gastroparesis or small intestinal bacterial overgrowth should be monitored regularly.

2. Digestive system symptoms and function in children with COVID-19: A meta-analysis

Wang J, Yuan X. Digestive system symptoms and function in children with COVID-19: A meta-analysis. Medicine (Baltimore). 2021 Mar 19;100(11):e24897. doi: 10.1097/MD.0000000000024897.

Patients with COVID-19 present with typical acute respiratory disease manifestations or even fatal respiratory failure. It is known that the entry of SARS-CoV-2 into human cells requires the ACE2 receptor and the gastrointestinal tract (GIT) and liver abundantly express ACE2. The fecal oral route mode of transmission is confirmed, also it has been shown that children's stool harbour SARS-CoV-2 for a longer period of time as compared to adults. This systemic review and meta-analysis highlight the various gastrointestinal and hepatological symptoms of COVID-19 in children as well as the prognosis. All the 19 included studies reported GIT symptoms. Sixteen studies (n=3120) reported diarrhea and the pooled prevalence was 10%. It was noted that children more than 5 years were more susceptible to diarrhea. Twelve studies (n=2466) reported nausea or vomiting with a pooled prevalence 7%. Four studies (n= 1843) reported abdominal pain with pooled prevalence 4%. Eight studies (n= 405, n-= 385) reported rise in ALT and AST with a pooled prevalence of 8% and 15% respectively. The recovery rate was 97 % as observed in five studies (n=400) and the pooled death rate was 1%.

3. Current and emerging therapies for coeliac disease

Kivelä L, Caminero A, Leffler DA, Pinto-Sanchez MI, Tye-Din JA, Lindfors K. Current and emerging therapies for coeliac disease. Nat Rev Gastroenterol Hepatol. 2021 Mar;18(3):181-195. doi: 10.1038/s41575-020-00378-1.

Gluten free diet (GFD) remains the essential pillar for the treatment of celiac disease and results in reduction of symptoms, and improvement in mucosal damage. Though 80-90% of children adhere to GFD but sometimes it is difficult due to hidden gluten in many products. And despite GFD persistence of symptoms and enteropathy is seen in almost 30 % and 60% respectively. This review provides a sketch of some newer therapeutic approaches other than GFD which have undergone clinical trials. Larazotide acetate is presently in phase III trial and is shown to block the intestinal epithelial permeability. Increase in intestinal permeability is one of the pathophysiology in celiac disease. It has shown promising results in phase I and II trials with reduction in gastrointestinal symptoms and diarrhea in celiac patients as compared to the placebo. The immunogenicity of gluten comes from the undigested protein component due to lack of protease enzyme. Many enzymes as protease and

peptidases are capable of degrading gluten. Prolyl endopeptidase is the most widely studied enzyme and is obtained from Aspergillus niger, Flavobacterium meningosepticum, Myxococcus xanthus and Sphingomonas capsulate. But before they come in the mainstream, they have to meet various criteria as stability in the gastrointestinal tract. Other enzymes under trail are STAN1, a cocktail of microbial enzymes; ALV003 a glutamine-specific cysteine endoprotease from germinating barley seeds etc. Interleukin 15 (IL-15) is involved in the key inflammatory process in celiac disease. Anti-IL-15, AMG 714 is a human monoclonal antibody and has shown promising results so far. Gluten tolerance can be achieved by targeting the antigens specifically the peripheral effector and/or memory autoreactive T cells. Nexvax 2 vaccine has antigen-specific tolerogenic effect and has the capability to reduce T cell response and is under trial. Another upcoming player in this category is tolerizing immune-modifying particles containing gliadin (TIMP-GLIA) which when administered is taken up by antigen presenting cells in liver and spleen and suppresses T and B cell response to gluten. ZED1227 is a very specific TG2 inhibitor. As TG2 is the key enzyme in the pathogenesis of celiac disease, inhibition of TG2 will lead to blockage of gliadin-induced proliferation of gliadin-specific T cells and prevent the T cell activation, and can also modulate intestinal epithelial permeability. Gliadin-reactive chicken yolk antibodies (AGY) and polymer BL-7010 or P(HEMA-co-SS) neutralise gliadin and reduces its absorption before it is digested as immunogenic peptide. BL-7010 has demonstrated prevention of gliadin absorption in well-controlled patients with coeliac disease. Several bacteria as Bifidobacterium longum CECT 7347, Bacteroides fragilis, Bifidobacterium breve etc have demonstrated the ability to modulate the intestinal permeability and decrease the adverse reaction of gluten.

4. The Present and Future Challenges of Wilson's Disease Diagnosis and Treatment

Leung M, Aronowitz PB, Medici V. The Present and Future Challenges of Wilson's Disease Diagnosis and Treatment. Clin Liver Dis (Hoboken). 2021 May 1;17(4):267-270. doi: 10.1002/cld.1041. PMID: 33968387; PMCID: PMC8087914.

This review gives run through of the current understanding of genetics and challenges in the management along with the future therapies of Wilson's Disease (WD). Wilson disease can present after 3 years of age predominantly with hepatic manifestations and after 10 years of age with neurological manifestations. Though the spectrum can range from asymptomatic transaminitis to severe liver failure or neurological impairment. In a recent analysis using genome sequencing the genetic prevalence has been reported as 1 in 7026 individuals which is much higher as compared to the previously reported clinical prevalence of 1 in 30,000 individuals. The diagnosis is based on low ceruloplasmin, increased 24-hour urinary copper excretion, liver biopsy and genetic testing for mutations in ATB7B gene. There is a lack of corelation between the genotype and phenotype which might be a consequence of interaction between the epigenetics and various metabolic factors. Though genetic testing in the framework of clinical and biochemical setting is diagnostic, but many tools of genetic analysis are not widely available and it requires interpretation by an expert geneticist. Radioactive copper incorporation is a new non-invasive modality with high sensitivity and specificity and is comparable with 24-hour urine copper estimation. In this the incorporation of intravenous bolus injection of ^{64}Cu tracer is measured in liver and serum and has good diagnostic accuracy. Relative exchangeable copper (REC), another non-invasive test is the ratio of exchangeable copper to total serum copper and is highly specific and sensitive for WD. There is impairment of mitochondrial functions in WD which is amenable to removal of copper but we don't have anti copper agents that act specifically on mitochondria or tools to monitor the response. Gene therapy is materialising as a promising modality. Incorporation of viral vector which is adeno-associated and expresses ATP7B transgene can correct copper metabolism in animal models.

Compiled by **Rimjhim Shrivastava**