Coagulation abnormalities in children with Celiac disease

We prospectively analyzed the coagulation abnormalities in 111 children with Celiac disease at diagnosis and its association with histology grade on duodenal biopsy; 27% had deranged prothrombin time. There was an increasing proportion of coagulopathy with progression of Marsh Grade on duodenal histology.

Keywords: *Coagulation profile, Malabsorption, Prothrombin time.*

Celiac disease is characterized by small bowel villous atrophy and malabsorption. Associated vitamin K deficiency leads to prolonged prothrombin time [1]. We conducted this study to analyze the coagulation profile of children with celiac disease and assess its association with Marsh grading on histology.

Children aged 6 month to 18 years with suspected celiac disease were included based on symptoms and serology. Children with prior administration of vitamin K or those already on gluten free diet (GFD) were excluded. Complete blood count, prothrombin time and activated partial thromboplastin time (aPTT) were tested prior to endoscopy. International normalized ratio (INR) <1.4 was considered as normal [1]. We categorized deranged INR as mild (1.40-2.50), moderate (2.51-5.0) and severe (>5.0) [2]. Abnormal aPTT was defined as the difference between test and control of more than 8 seconds. Normal platelet counts were 1.50-4.50 lakhs/cu.mm. Children with Marsh histology grade II/ III were started on GFD and favorable responses confirmed on follow-up to establish definitive diagnosis of Celiac disease. Children with moderate and severely deranged prothrombin time were given one dose of parenteral Vitamin K before procedure.

Out of 152 children, 111 (65 boys, 46 girls) were confirmed to have celiac disease. The mean age at presentation was 5.5 years, the youngest being 7 months and oldest 15 years. Thirty (27%) children had deranged INR; none had any significant bleeding. The proportion of deranged INR was found to be increasing with the severity of histological abnormalities (***Table* I**). Eighty-two (73.9%) children had normal platelet counts while thrombocytosis was seen in 26.1% children; 19% children had prolonged aPTT.

TABLE I INR IN DIFFERENT MARSH GRADES OF CELIAC DISEASE

INR	*Marsh grade 2 (n=9)*	*Marsh grade 3a (n=16)*	*Marsh grade 3b (n=29)*	*Marsh grade 3c (n=57)*	*Total (n=11)*
<1.40	8 (88.9)	13 (81.3)	23 (79.3)	37 (64.9)	81 (73.0)
≥1.40	1 (11.1)	3 (18.8)	6 (20.7)	20 (35.1)	30 (27.0)

INR: International normalized ratio; Values in No.(%).

Mitterstieler, *et al*. [3] reported four children with celiac disease who had hemorrhagic diathesis due to a low "prothrombin complex". After the administration of vitamin K1, there was an immediate rise in the prothrombin complex and bleeding was quickly stopped.

Most published guidelines on celiac disease recommend confirmation of the diagnosis of celiac disease by documenting villous atrophy on small intestinal biopsy and response to gluten-free diet [5]. In the presence of coagulopathy, thrombocytopenia or portal hypertension, diagnostic endoscopy and mucosal biopsy can cause significant bleeding [6]. Our study has a limitation that we could not demonstrate clinical significance of coagulopathy as none of our patient developed overt bleeding. This may be due to small sample size, and the vitamin K received before procedure may have partly corrected the prothrombin time.

We conclude that almost one-fourth of children with celiac disease have deranged INR before starting treatment, but they do not seem to develop bleeding following upper GI endoscopy.

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Glomerular Filtration Rate Estimation by Serum Creatinine or Serum Cystatin C in Preterm (<31 Weeks) Neonates

Glomerular filtration rate (GFR) was estimated by serum creatinine (Schwartz's equation) and serum cystatin C (Filler's equation) in preterm neonates (24-31 weeks of gestation) in a prospective cohort study. Serum creatinine and cystatin C was obtained at birth and then every two weeks during the first month. We found a poor fit between two methods, and a steadier GFR assessment by cystatin C.

Keywords: *Acute kidney injury, Diagnosis, Infants, Renal function tests.*

Accurate measurement of glomerular filtration rate (GFR) in preterm infants is difficult and frequently imprecise. Serum creatinine (SCr) based GFR is erratic due to its tubular secretion and reabsorption, changing muscle mass, bilirubin and fluid variations [1]. Serum Cystatin C is independent of muscle mass, bilirubin, age, sex, weight, or diet, and can be used to estimate GFR [2]. Cystatin C has been described as a better maker to estimate GFR than serum creatinine. However, very few studies have been conducted in preterm neonates <31 weeks [3,4]. To help us guide clinical decisions, we aimed to determine estimated GFR (GFR) by both methods.

This prospective cohort study was done at Vidant medical center Greenville, North Carolina after Institutional Review Board approval. We included neonates (24 to 31 weeks' gestational age) within 48 h of birth. We excluded neonates with confirmed sepsis, renal failure and prenatal congenital renal abnormalities. We estimated GFR at 48 hours of life, and on day 14 and day 28 of life. Cystatin C GFR was estimated by Filler's equation [log GFR=1.962+ [1.123xlog (1/cystatin C)], and creatinine based CGFR by schwartz equation [GFR=k × height/cr, k=0.33] [5]. Serum Creatinine was IDMS traceable and Cystatin C was measured by nephelometric immunoassay method using international reference materials. Both methods were compared by Bland Altman plots. Post-conceptional age was plotted against serum cystatin C- and creatinine-based eGFR.

Serum creatinine and Cystatin C was measured in 37 samples taken from 14 infants mostly (12/14) delivered by Caesarian-section. Out of 14 patients, 11 had received gentamicin for suspected sepsis in first 48 hours, and all had respiratory distress syndrome. Four patients had required dopamine for hypotension, and one patient had received indomethacin for hemodynamically- significant patient ductus arteriosus. Mean serum creatinine levels decreased steadily (P=0.007), and mean eGFR using creatinine increased (P=0.001) during first month (***Table* I, *Web Fig.* 1a**). Mean Serum cystatin C decreased from 1.39 mg/dL to 1.30 mg/dL (P=0.42). GFR estimated by cystatin C was significantly higher, and did not show much variability over time until the end of our observations (***Web Fig*. 1b,1c**). The poor fit was seen in the Bland Altman plot with the mean difference (Filler - Schwarz) around 25 with nearly all differences greater than 25 when the mean of the two measure was 50 or less and nearly all differences less than 25 when the mean was greater than 50 (***Web Fig*. 1d**).

In our study, serum creatinine and serum cystatin C levels decreased and eGFR increased with advanced postnatal age, possibly due to renal maturation [6]. This

TABLE I SERUM CREATININE AND CYSTATIN C VALUE AND CORRESPONDING GLOMERULAR FILTRATION RATE

Parameter	*Day of Life*		
	0-2 (n=14)	*14-16 (n=11)*	*28-30 (n=7)*
Cystatin C (Mean)	1.38	1.39	1.30
Cystatin C; Median (range)	1.38 (1.27-1.48)	1.35 (1.28-1.47)	1.34 (1.25-1.36)
GFR cystatin C	64.4	64.3	68.7
Serum Creatinine (Mean)[#]	0.63	0.43	0.29
Serum Creatinine (Median)	0.62	0.41	0.21
GFR creatinine (Mean)[#]	21.3	39.3	62.8

[#]P value significant (<0.05) between three recordings.