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New serological markers in pediatric patients with inflammatory bowel disease

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Abstract

The spectrum of serological markers associated with inflammatory bowel disease (IBD) is rapidly growing. Due to frequently delayed or missed diagnoses, the application of non-invasive diagnostic tests for IBD, as well as differentiation between ulcerative colitis (UC) and Crohn's disease (CD), would be useful in the pediatric population. In addition, the combination of pancreatic autoantibodies and antibodies against *Saccharomyces cerevisiae* antibodies/perinuclear cytoplasmic antibody (pANCA) improved the sensitivity of serological markers in pediatric patients with CD and UC. Some studies suggested that age-associated differences in the patterns of antibodies may be present, particularly in the youngest children. In CD, most patients develop stricturing or perforating complications, and a significant number of patients undergo surgery during the disease course. Based on recent knowledge, serum antibodies are qualitatively and quantitatively associated with complicated CD behavior and CD-related surgery. Pediatric UC is characterized by extensive colitis and a high rate of colectomy. In patients with UC, high levels of anti-CBir1 and pANCA are associated with the development of pouchitis after ileal pouch-anal anastomosis. Thus, serologic markers for IBD can be applied to stratify IBD patients into more homogeneous subgroups with respect to disease progression. In conclusion, identification of patients at an increased risk of rapid disease progression is of great interest, as the application of early and more aggressive pharmaceutical intervention could have the potential to alter the natural history of IBD, and reduce complications and hospitalizations.

Core tip: Application of non-invasive diagnostic tests for the diagnosis of inflammatory bowel disease (IBD) and differentiation between ulcerative colitis (UC) and Crohn's disease (CD) would be useful in the pediatric population. The combination of pancreatic autoantibodies and antibodies against *Saccharomyces cerevisiae* antibodies/perinuclear cytoplasmic antibody improved the sensitivity of serological markers in pediatric patients with CD and UC. In addition, serologic markers for IBD can be applied to stratify IBD patients into more homogeneous subgroups with respect to disease progression. With this knowledge, clinicians will be able to stratify patients accordingly with regards to the risk of disease progression, create a personalized treatment strategy, and attempt to modify disease course, thereby

improving long-term prognosis.

INTRODUCTION

Inflammatory bowel diseases (IBD), Crohn's disease (CD), and ulcerative colitis (UC) are chronic relapsing and remitting disorders of the digestive tract with unknown etiology[1]. Previous studies suggested that IBD results from an aberrant innate and acquired immune response to commensal microorganisms in genetically susceptible individuals[2,3]. This hypothesis is supported by the presence of antibodies directed to microbial antigens and by the identification of genetic polymorphisms, such as *NOD2/CARD15* and toll-like receptor 4 variants in CD[4]. Besides genetic predisposition and environmental factors, innate immunity is assumed to be another major contributor to pathogenesis in IBD.

Incidence of IBD is increasing, especially in pediatric patients with CD[5]. It is estimated that 15%-25% of IBD patients present in childhood. Recent studies showed that up to 20% of pediatric patients and 5%-15% of adult patients with colon only involvement had diagnostic difficulties if they had UC or colonic CD[6]. Serologic markers may help to establish diagnosis of IBD and to differentiate CD from UC, particularly when they are combined. It is especially important in the pediatric population, where invasive diagnostic testing is less desirable. In CD, most patients develop stricturing or perforating complications, and a significant number of patients undergo surgery during the disease course. Pediatric UC is more often associated with pancolitis and colectomy. Besides their diagnostic significance, current knowledge suggests that serologic markers can be a valuable aid in stratifying patients according to disease phenotype and risk of complications in IBD.

Several circulating autoantibodies have been described in IBD. The two most intensively studied conservative antibodies are atypical perinuclear anti-neutrophil cytoplasmic antibodies (atypical pANCA), which are primarily associated with UC and anti-*Saccharomyces cerevisiae* antibodies (ASCA), which are primarily associated with CD[4,7]. In pediatric IBD, sensitivity/specificity of pANCA in UC ranged between 57% to 83% and 65% to 97%, respectively, whereas in CD, ASCA showed a sensitivity/specificity in the range of 44% to 76% and 88% to 95%, respectively[8,9]. ASCA positivity or high titers are associated with complicated CD behavior (penetrating or stenosing disease) and could be useful markers for predicting the need for surgery in adults and children[10-12].

In pediatric studies, ASCA positivity increased with age at diagnosis[13] and was predictive for a more relapsing disease course [OR 2.9 (95%CI: 1.33-6.33)] in CD[14]. In addition, Trauernicht and Steiner[15] reported that serum ASCA antibodies are associated with lower anthropometric data (lower mean weight and height Z-scores) at the diagnosis of pediatric CD. pANCA is noted for its association with the "UC-like" phenotype in patients with CD[16,17]. Testing for ASCA and pANCA alone may have limited usefulness; therefore additional seromarkers are needed to improve the diagnosis, differentiation, and stratification of IBD, as well as prediction of disease course.

NEW SEROLOGICAL MARKERS

Crohn's disease

Antibodies to *Escherichia coli* outer membrane porin C, *Pseudomonas*-associated sequence I2, and bacterial flagellin CBir: Several antibodies against microbial components have been detected in serum samples of patients with IBD, including ones against outer membrane porin C (anti-OmpC) of *Escherichia coli*, against *Pseudomonas*-associated sequence I2 (anti-I2), and against bacterial flagellin CBir (anti-CBir1). Adherent-invasive *E. coli* has been found in ileal CD lesions, and OmpC has been shown to be required for these organisms to adhere to intestinal epithelial cells[18,19]. I2 was identified as a bacterial sequence from lamina propria mononuclear cells of active CD patients, and was shown to be associated with *Pseudomonas fluorescens*[20]. CBir1 is a flagellin related antigen that was initially identified in the gut flora of mice, and has the ability to induce colitis in immunodeficient mice[21].

Approximately 50% of adult patients with CD were positive for these markers, which were insignificant in adult patients with UC and healthy subjects[22,23]. The prevalence of anti-OmpC and anti-I2 was found to be 11% and 56% in pediatric CD, respectively[10,13,24-28]. The occurrence of antibodies varies in children of different ages: children younger than 8 years old at diagnosis are predominantly anti-CBir1 positive and ASCA and anti-OmpC negative, while those older than 8 are more commonly both ASCA and anti-CBir1 positive[13]. In children with CD, these strong serological responses to bacterial flagellin CBir antigens suggest that this antigen may have a potential role in the immunopathology of the disease.

Anti-glycan antibodies: The most recently described serum markers directed against microbial antigens are anti-glycan antibodies. Glycans are predominant cell surface oligosaccharides found on microorganisms, immune cells, erythrocytes, and tissue matrices. In IBD, the presence of anti-glycan antibodies results from the interaction between the immune system and the glycosylated cell wall components of such pathogens as fungi, yeast, and bacteria. Besides gASCA (which is very similar to conventional ASCA IgG), certain novel anti-glycan

antibodies were identified and associated with CD: anti-mannobioside carbohydrate antibodies (AMCA), anti-laminaribioside carbohydrate antibodies (ALCA), anti-chitobioside carbohydrate antibodies (ACCA), anti-laminarin carbohydrate antibodies (anti-L), and anti-chitin (anti-C) carbohydrate antibodies.

Anti-glycan markers are significantly increased in CD compared to UC and healthy controls[29,30]. However, only 16.9%-30.5% of patients were positive for each of AMCA, ALCA, ACCA, anti-L, and anti-C markers in pediatric CD[31]. Since the presence of anti-L and anti-C is low in ASCA-negative patients with CD, it has been proposed that these markers may bind different epitopes. Interestingly, the optimal cutoff values for anti-glycan markers were different in children than in adult populations in a serological study by Rieder *et al*[31]; strikingly lower cutoff points of gASCA, ACCA, ALCA, AMCA, anti-L, and anti-C were observed in children compared to adult patients with CD.

Pancreatic autoantibodies: Autoantibodies against exocrine pancreas (PAB) were described for the first time in 1984[32], but the autoantigenic targets of PAB were identified only in 2009[33,34]. The recognition of glycoprotein 2 (GP2) as a major target antigen of the droplet-like PAB (type I PAB) has been followed by the identification of CUB/zona pellucida-like domain-containing protein 1 (CUZD1) as another major antigenic target of PAB giving the reticulogranular, cytoplasmic pattern by indirect immunofluorescence (type II PAB). Both GP2 and CUZD1 are glycosylated membrane proteins residing in the acinar secretory storage granules of the pancreas. It was previously believed that GP2 is exclusively expressed by pancreatic acinar cells, but recent studies have shown that GP2 is also present as a specific membrane-anchored receptor on the microfold (M) intestinal cells of intestinal Peyer's patches, and is essential for host-microbial interaction and the initiation of bacteria-specific mucosal immune responses[35,36]. Notably, GP2 overexpresses at the site of CD inflammation in contrast to UC[33,37]. Respective data regarding CUZD1 expression in the intestine are sparse, with further research being needed to evaluate the relevance of these autoantibodies in CD. Combined determination of GP2 and CUZD1-specific autoantibodies by indirect immunofluorescence using recombinantly expressed human embryonic-kidney cell autoantigens represents a new method in the serological diagnosis of IBD. Discrimination between positive and negative reactions is considered to be easier in transfected cells than in primate tissues. The selective detection of anti-GP2 and CUZD1 autoantibodies by enzyme-linked immunosorbent assay (ELISA) has also been recently developed[34].

PAB have been reported to be pathognomonic markers of CD. A prevalence of 27% to 39% of PAB was present in patients with CD, compared with only 0% to 5% in patients with UC[38-40]. Increased prevalence of PAB has been found in unaffected first-degree relatives[41]. Stöcker *et al*[38] reported that PAB could only be determined in the serum of patients with CD. However, other studies found much higher (22%-24%) prevalence of PAB in UC[42-44]. Although anti-GP2 only represents a small proportion of PAB seropositive cases, anti-GP2 autoantibodies are detected in about 30% of patients with CD and in 5%-12% of patients with UC[45-47].

Ulcerative colitis
Autoantibodies against intestinal goblet cells: Serological markers have been far less extensively studied in UC than in CD. Autoantibodies against different colonic antigens have been found in patients with UC [*e.g.*, goblet cell autoantibodies (GAB)]. In previous studies, GAB has been detected in adult patients with UC, with a prevalence of 28% to 30%. In contrast, other studies suggested a much lower prevalence in both diseases[42-44]. These conflicting results are likely due to methodological differences, such as enzyme-linked immunosorbent assay antigen substrates and the evaluation of fluorescence patterns. GAB produce mucin that has multiple functions: it serves as a lubricant, provides nonspecific protection against unwanted microbial agents, and hosts the normal bacterial flora. Through complicated and strictly regulated glycosylation, mucins act as a decoy in binding a range of different microbes and maintaining the normal intestinal flora. The significance of these antibodies, however, has not been established and thus remains unclear.

DIAGNOSTIC VALUE OF NEW SEROLOGIC MARKERS IN IBD

In diagnostic workup of IBD, a serologic test with high sensitivity and specificity is desired. The diagnostic value of the new serologic markers for IBD is limited due to their low sensitivity and presence in other conditions, such as celiac disease, autoimmune diseases, and liver cirrhosis[48-50]. Sensitivity can be increased by the combination of different antibodies. A role for serological testing in screening for IBD was suggested by several studies, but the low sensitivity of these assays only provide a modest contribution to the identification of IBD[8,24,51-53]. The diagnostic value of the new serologic markers in children with IBD is shown in Table 1. A retrospective study of 300 pediatric patients tested in the IBD7 panel (anti-OmpC, anti-CBir-1, ASCA, and ANCA, Serology 7, Prometheus, Sandiego, CA, United States) for the evaluation of pediatric IBD resulted in a 67% sensitivity and 76% specificity. Consequently, this panel has a limited clinical utility in screening for pediatric IBD[53].

In pediatric CD, each anti-OmpC, anti-I2, or anti-CBir1 antibody was detected in 11%-55% of patients as a single marker. In a prospective pediatric study using combined analysis (anti-OmpC, anti-I2, anti-CBir1 or ASCA), 77% of patients with CD were positive for at least one microbial-driven antibody[26]. Therefore this method provided modest support for the diagnosis of CD.

Single glycan markers have limited clinical value for the primary diagnostic workup for CD due to their low

Table 1 Diagnostic value of the new serologic markers in children with inflammatory bowel disease

Marker	Sensitivity		Specificity	PPV	NPV	Ref.
	CD	UC	CD *vs* UC			
Anti-Omp	11%-34%	5%-25%	75%-95%	57.9%-69%	51.6%-53.3%	[8,24,25]
Anti-CBir	52%-56%	ND	ND	ND	ND	[10,13,26]
Anti-I2	44.4%-50%	41.7%-42%	58%-58.3%	51.6%-54.3%	51.1%-53.7%	[27,28]
gASCA	60.7%-62.7%	11.1%-14.6%	85.4%-88.9%	87.1%-92.5%	52.2%-55.9%	[30[1],31]
ACCA	8.7%-22%	3%-18.5%	81.5%-97%	72.2%-83.3%	32.4%-38.2%	[30[1],31]
ALCA	19.7%-30.5%	7.6%-14.8%	85.2%-92.4%	81.8%-81.6%	35.9%-40.1%	[30[1],31]
AMCA	12.2%-16.9%	7.6%-14.8%	85.2%-96.7%	71.4%-86.3%	31.9%-39.06%	[30[1],31]
Anti-L	18%-22%	3.3%-14.8%	85.2%-96.7%	76.5%-90.3%	33.3%-40.07%	[30[1],31]
Anti-C	10.2%-22%	2.3%-14.8%	85.2%-97.7%	76.5%-83.3%	33.3%-38.8%	[30[1],31]
PAB	34%-38.5%	20.4%-20.6%	79.4%-79.6%	62.5%-65.1%	54.7%-56.5%	[44,45[1]]
Anti-GP2	30.2%	8.8%	91.2%	77.4%	56.7%	[45][1]
GAB	12.2%	1.9%	98.1%[2]	86.5%[2]	52.7%[2]	[44]

[1]Mixed pediatric and adult cohort; [2]Ulcerative colitis (UC) *vs* Crohn's disease (CD). ND: No data available; Anti-OmpC: Antibodies against outer membrane porin C of *Escherichia coli*; Anti-CBir1: Antibodies against bacterial flagellin CBir1; Anti-I2: Antibodies against the *Pseudomonas*-associated sequence; ASCA: Antibodies against *Saccharomyces cerevisiae*; AMCA: Anti-mannobioside carbohydrate antibodies; ALCA: Anti-laminaribioside carbohydrate antibodies; ACCA: Anti-chitobioside carbohydrate antibodies; Anti-L: Anti-laminarin carbohydrate antibodies; Anti-C: Anti-chitin carbohydrate antibodies; PAB: Pancreatic antibodies; Anti-GP2: Antibodies against glycoprotein 2; GAB: Antibodies against intestinal goblet cells; IBD: Inflammatory bowel disease; PPV: Positive predictive value; NPV: Negative predictive value.

sensitivity. From the entire panel, gASCA came out as the most accurate for the diagnosis of pediatric CD (sensitivity: 62.7%, specificity: 95.6% CD *vs* controls, and 88.9% CD *vs* UC)[31]. With respect to the latest two novel markers, the addition of Anti-L and Anti-C to gASCA and pANCA further improved discrimination between CD and UC (*P* < 0.001) in a large pediatric and adult cohort with IBD (*n* = 818, 517 CD, 301 UC)[30]. More specifically, nearly three-quarters of the patients with CD showed seropositivity for at least one of the aforementioned seven anti-glycan antibodies[30,31]. Anti-glycan antibodies may be particularly important in ASCA-negative patients with CD. Rieder *et al*[31] found that 40.9% of ASCA-negative pediatric patients with CD were positive for at least one other anti-glycan marker, suggesting that these novel antibodies may further improve serological diagnosis for CD. Similarly, other studies found that about half of ASCA negative adult patients were positive for ALCA, ACCA, or AMCA[29,54]. In concordance with the results published by Rieder *et al*[55], Seow *et al*[30] demonstrated that all the anti-glycan antibodies were highly specific for IBD, particularly for CD (85.4%-97.7%), and were more prevalent in CD *vs* UC (*P* < 0.0015). In this large pediatric and adult cohort with IBD, anti-C showed the highest specificity of 97.7, followed by ACCA at 97%, then anti-L at 96.7%. Due to the combined use of these markers, the specificity for CD increases up to 100%[29,55].

While the specificity of PAB for CD is high, its sensitivity is low. In our study the presence of PAB was significantly higher in CD (34%) and UC (20.4%) compared with the pediatric control cohort (0%, *P* < 0.0001). Specificity of PAB was 100%; however, sensitivity was low. The combination of PAB and antibodies against ASCA/pANCA improved the sensitivity of serological markers in CD (87.4%) and in UC (79.6%); specificity was 89.3% and 93.2%, respectively[44]. Combinations of these antibodies, particularly with ASCA, have shown

increased sensitivity; therefore, it may be recommended in the diagnostic procedure of IBD[42,44]. Diagnostic accuracy of the combined novel antibodies with conventional serological markers in children with IBD is shown in Table 2[44].

In a recent study, Bogdanos *et al*[45] observed a significantly higher prevalence of PAB compared to anti-GP2 in UC (20.6% *vs* 8.8%, *P* < 0.003), whereas the difference between PAB and anti-GP2 did not reach a statistically significance level in CD (38.5% *vs* 30.2%, *P* = 0.108), respectively. Thus, anti-GP2 testing by ELISA assay seems to be more specific for CD than for PAB testing, so it may improve the differentiation between CD and UC.

In UC, the most frequently studied serological marker is pANCA. Besides pANCA, in our study the prevalence of GAB was significantly increased in patients with UC in comparison to CD and controls (UC, 12.2%; CD, 1.9%; controls, 1.9%; *P* = 0.02). Sensitivity can be significantly increased with combinations of different antibodies. For example, pANCA and/or GAB together had a sensitivity of approximately 80% for UC[44].

ASSOCIATION WITH IBD PHENOTYPES AND PROGNOSIS

In patients with CD at diagnosis, most patients have inflammatory type disease[56,57]. Nevertheless, during the disease course the development of complicated behavior in the pediatric population is a common feature[58]. In the largest pediatric cohort with CD (*n* = 989), the cumulative incidence of stricturing or penetrating complications was found to be 13%, 27%, and 38%, 1, 5, and 10 years after the diagnosis of IBD, respectively[58]. Furthermore, small bowel disease is more frequently correlated with the development of complicated disease behavior than in isolated colonic disease. Based on these observations,

Table 2 Diagnostic accuracy of the combined novel antibodies with conventional serological markers in children with inflammatory bowel disease[44,45]

	Marker	Sensitivity	Specificity	PPV	NPV	Ref.
CD *vs* controls	ASCA	35.5%-72.8%	95.2%-96.5%	91%-93.8%	59.9%-77.8%	[44,45[1]]
	PAB	34.0%-43.8%	100%	100%	60.2%	[44,45[1]]
	Anti-GP2	30.2%	96%	88.3%	57.9%	[45]
	pANCA	33.0%	94.2%	85.1%	58.4%	[44]
	GAB	1.9%	98.1%	50.0%	50.0%	[44]
	PAB and/or ASCA	79.6%	95.2%	94.3%	82.3%	[44]
	Anti-GP2 and/or ASCA	50.9%	92.9%	87.8%	65.4%	[45]
	PAB and/or ASCA and/or pANCA	87.4%	89.3%	89.1%	87.6%	[44]
	PAB and /or ASCA/ pANCA-	53.4%	95.2%	91.8%	67.1%	[44]
	ASCA+/pANCA-	51.5%	95.2%	91.5%	66.2%	[44]
UC *vs* controls	pANCA	77.5%	94.2%	93.0%	80.9%	[44]
	GAB	12.2%	98.1%	86.5%	52.8%	[44]
	PAB	20.4%-23.5%	100%	100%	55.6%	[44,45[1]]
	Anti-GP2	8.8%	96%	68.8%	51.3%	[45][1]
	ASCA	6.9%-26.5%	95.2%-96.5%	66.3%-84.7%	50.9%-56.4%	[44,45[1]]
	ASCA[2]	16.3%	95.2%	77.3%	53.2%	[44]
	PAB and/or pANCA	79.6%	94.2%	93.2%	82.2%	[44]
	PAB and/or pANCA and/or GAB	79.6%	94.2%	93.2%	82.2%	[44]
	Anti GP2 and/or ASCA	14.7%	92.9%	67.4%	52.1%	[45]
	GAB+/pANCA+	12.2%	98.1%	86.5%	52.8%	[44]
	PAB+/pANCA+	18.4%	100%	100%	55.1%	[44]
	rPAB+/pANCA+	22.4%	100%	100%	56.3%	[44]
	GAB+/PAB+/pANCA+	4.1%	100%	100%	51.0%	[44]

[1]Mixed pediatric and adult cohort; [2]Diagnostic value of antibodies against *Saccharomyces cerevisiae* (ASCA) antibodies in ulcerative colitis (UC) patients without primary sclerosing cholangitis (PSC). PAB: Pancreatic antibodies; Anti-GP2: Antibodies against glycoprotein 2; pANCA: Perinuclear anti-neutrophil cytoplasmic antibodies; GAB: Antibodies against intestinal goblet cells; IBD: Inflammatory bowel disease; CD: Crohn's disease; PPV: Positive predictive value; NPV: Negative predictive value.

a more aggressive treatment should be considered in this large subgroup of pediatric patients with CD. Consequently, the evaluation of relevant phenotype-serotype correlations may provide important prognostic information. Association of the new serologic markers with phenotype in pediatric CD is summarized in Table 3.

Antibodies directed to bacterial antigens were reported as being qualitatively (presence) and quantitatively (titer) associated with aggressive disease behavior in both children and adults[10,26,59,60]. The first prospective pediatric study conducted by Dubinsky and co-workers demonstrated that the degree of the immune response to ASCA, anti-I2, anti-OmpC, and anti-CBir1 correlated with internal penetrating, stricturing disease, and the need for surgery in a large cohort with CD (*n* = 196). The risk of developing penetrating and/or stricturing CD was increased 11-fold in those subjects with immune responses to all four antigens (anti-12, anti-OmpC, anti-CBir1, and ASCA) compared to seronegative cases (OR = 11, 95%CI: 1.5-80.4, *P* = 0.03). Moreover, in this study, the highest antibody sum group and quartile sum score group showed the most rapid disease progression[26]. These initial findings were confirmed in another larger study of 796 pediatric CD patients using ASCA, anti-OmpC, and anti-CBir1[10].

Recent studies demonstrated that seropositivity for anti-glycan antibodies was associated with early disease onset, small bowel disease, complicated disease behavior, and CD-related surgery in both adult and pediatric

CD[4,29,30,31,54,55,61,62]. This was also found in both qualitative (number of positive antibodies) and quantitative (antibody titers) immune response. In a cross-sectional pediatric study, ALCA and anti-L had the strongest association with complications[31]. In this pediatric population, most of the anti-glycan markers, except for ACCA and anti-C, were associated with complicated disease behavior and ALCA with CD-related surgery. Only gASCA was associated with terminal ileal disease location. Surprisingly, gASCA was inversely correlated with early disease onset in this pediatric cohort[31], but this link was found to be positive in adult CD[4,55,63]. This difference may arise from the distinct nature of the intestinal immune system in children.

There are conflicting results related to the association between PAB and CD phenotype in adult cohorts. Increased prevalence of PAB was observed in patients with early onset of disease, and stricturing or penetrating phenotypes[39,40,42,43,64]. Lakatos *et al*[42] reported an association between PAB positivity, perianal disease, and EIMs. However, in our pediatric study, we found that the presence of PAB was not associated with disease phenotype in CD[44]. It is difficult to compare the data of these studies, since age may affect localization and behavior as well.

In some studies, the relation between anti-GP2 and CD phenotype was also evaluated. In mixed pediatric and adult cohort with CD (*n* = 169), humoral autoreactivity to GP2 and ASCA applying ELISA has been reported to be associated with ileocolonic location, suggesting a

Table 3 Association of the new serologic markers with phenotype in pediatric Crohn's disease

Marker	CD phenotype	Ref.
Anti-OmpC	Complicated disease behavior	[10,26]
Anti-CBir1	CD-related surgery	
Anti-I2		
ASCA		
gASCA	Early disease onset	[30[1],31]
	Ileal disease location	
	Complicated disease behavior	
	Perianal disease	
	CD-related surgery	
ACCA	Complicated disease behavior CD-related surgery	[30][1]
ALCA	Ileal disease location	[30[1],31]
	Complicated disease behavior CD-related surgery	
AMCA	Complicated disease behavior	[30[1],31]
	perianal disease	
Anti-L	Ileal disease location	[30[1],31]
	Complicated disease behavior	
	Perianal disease	
	CD-related surgery	
Anti-C	Complicated disease behavior	[30][1]
	Perianal disease	
	CD-related surgery	
Anti-GP2 with ASCA	Early disease onset	[45][1]
	Ileal location	
	Complicated behavior	
	Perianal disease	

[1]Mixed pediatric and adult cohort. Anti-OmpC: Antibodies against outer membrane porin C of *Escherichia coli*; Anti-CBir1: Antibodies against bacterial flagellin CBir1; Anti-I2: Antibodies against the *Pseudomonas*-associated sequence; ASCA: Antibodies against *Saccharomyces cerevisiae*; AMCA: Anti-mannobioside carbohydrate antibodies; ALCA: Anti-laminaribioside carbohydrate antibodies; ACCA: Anti-chitobioside carbohydrate antibodies; Anti-L: Anti-laminarin carbohydrate antibodies; Anti-C: Anti-chitin carbohydrate antibodies; Anti-GP2: Antibodies against glycoprotein 2.

role for GP2 as a receptor on M cells in intestinal Peyer's patches[45]. Moreover, in this cohort, the presence of anti-GP-2 was associated with younger age at the onset of the disease (< 16 years), stricturing behavior, and perianal disease in CD[45]. Similarly, Pavlidis *et al*[46] demonstrated that patients with colonic CD do not show significant antibody reactivity against GP2 compared to those who had ileal localization; the site of GP2-rich M cells. However, a Belgian study by Op De Beéck *et al*[65] did not find any association between anti-GP2 seropositivity and clinical phenotype in CD (*n* = 164) using the same ELISA.

In patients with UC, both anti-CBir1 and pANCA positivity correlated with the development of pouchitis after ileal pouch-anal anastomosis. In a study by Fleshner *et al*[66], diverse patterns of reactivity to microbial antigens were manifested as different forms of pouchitis (*n* = 238, age range: 8-81 years). Anti-CBir1 positivity indicated acute pouchitis only in patients who have low-level pANCA expression, with increased incidence of chronic pouchitis only in patients who had high-level pANCA expression. In a meta-analysis by Singh *et al*[67], the risk of chronic pouchitis after IPAA was higher in ANCA-positive patients, but the risk of acute pouchitis was unaffected by ANCA status. These data had a significant influence on the patients' treatment in post-operative course. The studies could not demonstrate any association between the presence of GAB and clinical presentation, medical therapy, or need for surgery in patients with UC.

ASSOCIATION WITH THE RESPONSE TO THERAPY AND DISEASE ACTIVITY

Recent studies have highlighted the connection of serologic markers with biologic therapies. Previous studies demonstrated that ASCA signals do not predict response to anti-tumor necrosis factor (TNF)-α therapies in CD[4,68]. Comparative findings were reported regarding the effect of biological agents in the behavior of anti-GP2 antibodies. Belgian investigators did not find a robust effect of infliximab and adalimumab in patients followed up for 6-44 mo[65].

No association was detected between anti-glycan markers and the response to corticosteroids and disease activity in children with CD[31]. Similarly, in our study, we could not find any association between serum antibodies of PAB, ASCA, and ANCA and response to therapy[44].

Dubinsky *et al*[69] reported that a combination of phenotype, serotype, and genotype is the best predictive model of non-response to anti-TNFα agents in pediatric patients. In this study, anti-OmpC, anti-CBir1, anti-I2, ASCA, and pANCA serum markers were analyzed. The most predictive model included the presence of three novel "pharmacogenetic" loci, the previously identified BRWD1, pANCA, and UC diagnosis (P < 0.05). The relative risk of non-response increased 15-fold when the number of risk factors increased from 0-2 to $\geq$ 3 (P < 0.0001)[69].

Based on longitudinal analysis, the presence of antibodies in IBD is relatively constant during the disease course[62,70]. However, the prevalence of ASCA, anti-OmpC, and anti-I2 has been found to be more frequent when the disease persists for a long time[12,60]. Furthermore, disease activity, CRP levels, or response to corticosteroids does not appear to influence marker levels in longitudinal studies. Therefore, serial measurement of antibodies may not provide additional information for the evaluation of IBD[31,70].

CONCLUSION

The correct diagnosis and classification of IBD as either CD or UC is essential for choosing the appropriate therapy. Combined application of the novel antibodies (PAB/GP2) with conventional serology markers (ASCA/pANCA) increased sensitivity. Therefore, the use of combinations may be advisable in the diagnostic work-up of selected cases. Moreover, childhood-onset CD often leads to complicated disease (stricturing or penetrating) with increasing prevalence in parallel to disease duration.

In CD, information gained from a serologic profile, both qualitatively and quantitatively, may help to determine the likelihood of a more severe phenotype. In addition, pediatric UC is associated with pancolitis and a higher risk of colectomy. In patients with UC, serologic markers are associated with the development of pouchitis after ileal pouch-anal anastomosis. With this knowledge, clinicians will be able to stratify patients regarding the risk of disease progression, create a personalized treatment strategy, and try to modify disease course, thus improving long-term prognosis. Further simultaneous prospective multicentric studies are needed to evaluate the exact prognostic role of serologic markers which may help in the individual therapeutic management of pediatric and adult IBD.

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