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How Does Knowledge from Translational Research Impact Our Clinical Care of Pediatric Inflammatory Bowel Disease Patients?

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Abstract

Recent translational studies have provided new insights into pathogenesis, disease behavior, and treatment responses in pediatric Inflammatory Bowel Disease (IBD). Registry studies have identified distinct clinical phenotypes with increasing age of onset; this has led to a revision of the clinical phenotyping system, now termed the Paris classification system. It is recognized that there are infantile (age <2 years), very early onset (VEO, age 2-10), and early onset (EO, age 10-17) forms of disease. Rare genetic mutations affecting anti-microbial and anti-inflammatory pathways have been discovered in infantile and VEO forms, while genetic pathways identified in EO disease have been similar to adult-onset IBD. Genetic and serologic patterns measured soon after diagnosis have been shown to be associated with more aggressive stricturing behavior; these patterns may now be used clinically to help predict disease course. More recently, clinical and genetic models have been developed that, if validated, could be used to predict treatment responses.

Keywords

ASCA; ANCA; OmpC; I2; CBir1; NOD2; infantile; very early onset; early onset; Crohn disease; Ulcerative Colitis; microbiome; dysbiosis; serology; diagnosis; prognosis; stricture; Paris

Introduction

Recent translational studies have provided new insights into pathogenesis, disease behavior, and treatment responses in pediatric Inflammatory Bowel Disease (IBD). Registry studies have identified distinct clinical phenotypes related to age of onset. It has been recognized that younger children are more likely to have isolated colonic disease, with small bowel involvement approaching the frequency identified in adult-onset disease after age 10. Moreover, children with either Crohn disease (CD) or Ulcerative Colitis (UC) consistently have been shown to exhibit more extensive disease than those with adult onset IBD, and to experience a more aggressive course complicated by high rates of early surgery, as well as by growth failure.

Infantile (< age 2), very early onset (VEO, < age 10), and early onset (EO, age 10-17) forms of disease are now recognized. Rare genetic mutations affecting anti-microbial and anti-inflammatory pathways have been discovered in infantile and VEO forms, while genetic pathways identified in EO disease have been similar to adult-onset. Particular genetic and serologic patterns measured soon after diagnosis have been shown to be associated with more aggressive stricturing behavior; these patterns may now be used clinically to help predict disease course. Importantly, though, the frequency of genetic mutations and particular serologic titers used to develop these prognostic models have now been shown to vary with age of onset. Therefore, it will be important to validate these models in the VEO and EO pediatric age groups.

To address the need to validate genetic and serologic models of disease behavior in the pediatric age group, the RISK study, a prospective inception cohort study sponsored by the Crohns and Colitis Foundation of America (CCFA), has now enrolled 1200 pediatric CD patients and 100 UC patients at the time of diagnosis at 28 centers across North America. Results from RISK will be used to validate existing models for structuring or internal penetrating behavior, and to discover new pathogenic mechanisms and prognostic biomarkers. More recently, clinical and genetic models have been developed, which if validated could be used to predict treatment responses, including the response to infliximab therapy. Data from RISK comparing the effectiveness of specific therapies in precisely defined patient subsets will be critical in testing the accuracy of these models of treatment response, and thereby guiding clinical care in the future.

New Clinical Phenotyping Guideline: The Paris Classification System

Increased awareness of clinically important sub-types of pediatric IBD has led to a suggested revision of the clinical phenotyping system. This new guideline for phenotyping pediatric-onset patients is termed the Paris classification system [1•]. The most important modification introduced by this system is to refine the range for age-of-onset in pediatric IBD: A1a, age < 10 years, and A1b, age 10 to < 17 years. Recognizing the unique features of extensive small bowel disease, the L4 modifier for disease proximal to the terminal ileum has also been refined, to L4a for disease proximal to the ligament of Trietz, and L4b for disease from the ligament of Trietz to the terminal ileum. Complicated stricturing (B2) or internal penetrating (B3) behavior will now be included in one B2B3 category, and the unique pediatric complication of growth failure will be denoted by G1. Finally, recognizing the important prognostic implications of a severe bout of UC, those who have experience this at any time will be denoted S1. It will be important that future translational studies, outcome registries, and clinical trials report results using this new classification system.

Pathways Identified by Genetic Studies of Infantile and VEO IBD

A number of recent case series of infantile and VEO IBD have identified rare loss-of-function mutations in key immune genes leading to severe disease (see Table 1). Mutations in the IL-10 receptor (IL-10) which abrogate anti-inflammatory IL-10 signaling have been described specifically in colitis presenting in the first year of life [2]. IL-10 ordinarily suppresses bacterial product dependent production of pro-inflammatory cytokines by

monocytes; this anti-inflammatory effect is profoundly suppressed in infants with IL-10R mutations and colitis. This leads to high production of cytokines, including TNF α , and a severe disease course refractory to medical therapy. Allogeneic stem cell transplantation may be required to induce disease remission in these patients. Currently, screening can be performed via research assays involving IL-10 stimulation of peripheral blood mononuclear cells (PBMC), followed by sequencing for the *IL-10R* mutations [2]. However, it should be noted that a recent comprehensive analysis of 75 children with IBD, including 13 infants, confirmed loss of IL-10 signaling due to IL-10R mutations in only 2 of the infants, suggesting that this will be a rare pathogenic mechanism restricted to some infantile forms of IBD [3].

Mutations in the *XIAP* gene also have recently been reported to be associated with infantile or VEO colitis that may mimic idiopathic IBD [4]. Up to 20% of patients with XIAP deficiency will develop IBD; this may be due to combined defects in ant-microbial responses and regulatory T cell functions. Importantly, these patients are at high risk for development of life-threatening viral-induced hemophagocytic lymphohistiocytosis. Allogeneic stem cell transplantation may be required to induce disease remission and prevent mortality from hemophagocytic lymphohistiocytosis. Testing for this condition is via a flow cytometry-based assay that measures expression of the XIAP protein on white cells (<http://www.cincinnatichildrens.org/service/c/cancer-blood/hcp/diagnostic-lab/tests/>).

A series of very young patients with Dyskeratosis Congenita have recently been described who initially presented with lymphopenia, hypogammaglobulinemia, recurrent infections, and VEO severe enterocolitis [5]. This disorder is characterized by premature telomere shortening, which may lead to a reduction in the stem cell compartment supporting lymphocytes and intestinal epithelial cells, and thereby produce the clinical phenotype of immune deficiency and IBD. Screening can be accomplished via measurement of telomere length in PBMC (<http://repeatdiagnostics.com/>). Allogeneic stem cell transplantation is indicated for bone marrow failure and recurrent infections, but may not alleviate symptoms of IBD.

Genome-wide-association studies of CD and UC in EO (all patients < age 17) with IBD did not yield unique susceptibility genes compared to similar studies of adult-onset patients [6-9]. Collectively, these studies have suggested that common variants with a modest effect upon overall disease risk are largely independent of age of onset between the EO (10-17) and adult onset groups. However, a recent study limited to VEO CD did identify a novel rare variant in the *NCF2* gene that would be predicted to affect the NADPH oxidase complex, and thereby phagocyte killing of microbes [10•]. Remarkably, this is the same complex in which genetic mutations cause the primary immune deficiency disorder chronic granulomatous disease (CGD), which is in turn often associated with VEO IBD. This information has important implications for future adequately powered studies in the VEO sub-group, and for therapies designed to stimulate microbial killing in those with mutations reducing NADPH oxidase complex function.

A More Common Cause for Reduced Innate Function in CD: Granulocyte-Macrophage Colony Stimulating Factor Auto-antibodies (GM-CSF Ab)

While rare genetic mutations recently identified in VEO IBD have provided valuable insights into fundamental mechanisms of disease, these are less likely to contribute to pathogenesis in the more common cases with older age of onset. Because mild reductions in neutrophil function had recently been described in adult-onset CD, and high titers of neutralizing GM-CSF Ab had been shown to impair phagocyte antimicrobial function in the rare lung disease pulmonary alveolar proteinosis, we asked whether more modestly elevated titers of GM-CSF Ab would be present in IBD [11, 12]. We discovered that GM-CSF Ab are present in a subset of CD patients, and that titers increase with increasing age of onset, from VEO to EO pediatric disease, and further with adult-onset disease [13•]. Overall, approximately fifty percent of CD patients exhibit high levels of GM-CSF Ab which are associated with reduced neutrophil phagocytic capacity, increased intestinal permeability and reactivity to the enteric flora, and expansion of effector T cells expressing the gut homing receptor CCR9 [13•-15]. This information is of potential therapeutic interest, as an oral small molecule inhibitor of CCR9 is entering phase 3 clinical trials for CD, and we have found that CD patients with elevated GM-CSF Ab who are treated with current therapies progress more rapidly to stricturing behavior requiring surgery [16]. Moreover, as GM-CSF itself has been tested as a therapy in CD, with some patients achieving remission, this raises the possibility that GM-CSF Ab titers might be used to predict which CD patients would derive the greatest benefit from GM-CSF administration [17, 18]. Overall, the concept that endogenous cytokine auto-antibodies regulate inflammation in IBD is new and highly relevant, given the advent of therapeutic monoclonal anti-cytokine antibodies.

Alterations in the Microbiota in Pediatric IBD

Previous studies performed in mice genetically susceptible to developing spontaneous colitis demonstrated that colitis would not occur in the absence of the enteric flora. This finding suggested that antigens derived from the enteric flora could drive the development of IBD in humans. The identification of genetic variation in *FUT2* as a risk factor for pediatric and adult CD, and for increased mortality in premature infants with necrotizing enterocolitis, was therefore of great interest [19, 20]. The *FUT2* gene product, fucosyltransferase 2, is known to regulate bacterial colonization of the gut; thus the *FUT2* risk variant may influence CD and necrotizing enterocolitis pathogenesis by leading to altered intestinal microbiota. Alpha-defensins are paneth cell products which are important for host defense in the gut. Alpha-defensin-5 (HD-5) has now been shown to be suppressed in the ileum of pediatric CD patients, independent of inflammation [21]. This suppression may contribute to local invasion of commensal bacterial species. Conversely, the degree of local inflammation was associated with the level of up-regulation of Paneth cell HD-5 in the colon of pediatric CD patients.

Several recent studies using modern molecular techniques have begun to define differences in the microbiome (“dysbiosis”) in children with IBD. Most studies have shown evidence for altered flora in CD, but not UC. An expansion of adherent-invasive *E. Coli* (AIEC) has been consistently noted in patients with CD, together with a reduction in *F. prausnitzii* [22•,

23]. In tissue culture and animal models, colonization with AIEC has been shown to promote epithelial injury and colitis, suggesting that it may also drive disease in humans [24]. In animal studies, flagellin has been identified as a critical virulence factor for colitis, and a potent antigen for elicitation of effector T cell responses in both animal models and patients with IBD [25]. In vitro studies using cell lines have shown that AIEC strains will induce pro-inflammatory TNF α and IL-8 expression, and damage the epithelial barrier [22•, 24]. Remarkably, the oral microbiome in children with CD, but not UC, has recently been shown to exhibit reduced diversity, suggesting that clinical sampling of this more accessible site may provide important insights into dysbiosis in IBD [26]. It will be important in future studies to account for genetic and acquired differences in host innate immunity which may promote dysbiosis.

Dysregulated Immune Responses to the Normal Enteric Flora in CD

In contrast to the evidence for dysbiosis in IBD, many IBD patients may exhibit enteric flora similar to that of healthy individuals, but a dysregulated host response to these normal commensals. Two recent studies have illustrated aberrant inflammatory responses to commensals specifically in pediatric CD patients. In the first, IL-8 secretion was induced in ileal or colon biopsies of CD patients exposed to *B. thetaiotaomicron*; there was no effect on biopsies from healthy controls [27]. Similarly, candida induced both IFN γ and IL-17 production by CD, but not UC or control, peripheral blood mononuclear cells [28]. Collectively, these studies provide a rationale for the use of antibiotics, probiotics, or prebiotics to regulate components of the enteric flora which may be driving mucosal immune responses in selected IBD patients. However, clinical tools to define elements of the flora which are driving disease in individual patients are currently lacking, making rationale use of these approaches challenging.

Chronic inflammation in IBD is believed to be ultimately driven by polarized T cells reactive in part to enteric antigens. These T cells can include Th1 cells which produce IFN γ ; Th17 cells which produce IL-17; or Th2 cells which produce IL-4, IL-5, or IL-13. A recent pediatric study has identified intriguing variation in expression of Th1 and Th17 cytokines as a function of both intestinal inflammation and location [29]. IL-17A was shown to be highly expressed in healthy ileum. With the onset of inflammation, both IL-17A and IFN γ were induced in CD ileum, while IL-17A was induced in UC colon, and IFN γ in CD colon. These findings may have implications for treatment of extensive disease involving the ileum and colon, which is typically the case in pediatric CD, using monoclonal antibodies targeting only Th1 or Th17 pathways. Moreover, several studies found an atypical Th2 polarization in UC, with up-regulation of IL-13 leading to epithelial dysfunction [30]. This IL-13 upregulation may have implications for development of new therapies targeting IL-13 in UC, as was recently reported for a clinical trial of IFN β -1a, which suppressed IL-13 and improved symptoms in adults with UC [31]. It is likely that clinical assays to measure tissue cytokine profiles will be required to translate this knowledge of intestinal T cell polarization to the clinic, and ultimately to guide use of specific biologic therapies.

Serologic Responses to the Enteric Flora and Complicated Disease Behavior in CD

A large body of work now supports the concept that a sub-set of CD patients develop long-lasting IgA and IgG antibodies targeting commensal flora, and that high titers of these antibodies are associated with more rapid progression to stricturing or internal penetrating behavior [32]. Studies in the past year have shown that genetic mutations that reduce neutrophil antimicrobial function in patients with CGD or glycogen storage disease 1b (GSD1b) are sufficient to lead to high titers of anti-microbial serologies (AMS) [33, 34]. These serologies include the AMS previously linked to complicated CD, including ASCA, OmpC, I2, and CBir1 (see Table 2). Remarkably, high titers of AMS were observed even in CGD or GSD1b patients who lacked intestinal inflammation. Consistent with this, we have found that AMS are also elevated in CD patients with high GM-CSF Ab [13•]. Studies in animal models have shown that GM-CSF Ab promote more severe NSAID-induced ileitis, while immunization to flagellin (e.g., CBir1 Ab) promotes more severe dextran sodium sulfate-induced colitis [13•, 35•]. Therefore, at least the GM-CSF and CBir1 Ab may be directly involved in disease pathogenesis, as well as serving as biomarkers for more aggressive disease. Interestingly, CBir1 titers tend to be higher in children with CD younger than 10 years old, while GM-CSF Ab and ASCA titers are increased in the 10-17 age group [36•], suggesting distinct microbial and immune mechanisms of disease in the VEO (A1a) and EO (A1b) groups.

A large pediatric cohort study has confirmed the strong association between high titers of AMS and more rapid progression to stricturing or internal penetrating behavior previously reported in adults [32]. Importantly, AMS in this prospective cohort study were measured close to the time of diagnosis, and so were predictive of the progression from the initial inflammatory phenotype to the stricturing/penetrating phenotype. The CCFA-sponsored RISK study will seek to validate this association in 1200 children with CD enrolled at the time of diagnosis, and to identify additional factors which will improve the positive-predictive value of the current AMS panel, which is approximately 50% for patients with five-year duration of disease [13•, 32].

A recent adult study confirmed the prior observation in pediatric-onset disease that the presence of a *NOD2* mutation increases the risk for complicated disease behavior for each level of AMS titers, and that the ANCA biomarker is associated with reduced risk for stricturing/penetrating behavior [37, 38]. For each predicted level of risk, there was excellent agreement between the modeled and actual outcomes ($r=0.973$), with the area-under-the-curve for the receiver operator curve being equal to 0.801. Therefore, this model for stricturing/internal penetrating behavior, which includes the *NOD2* genotype, AMS titers, and ANCA, provides sufficient accuracy for use in clinical practice.

These parameters can now be measured as part of a commercial panel, the Crohn's Prognostic Test, offered by Prometheus Labs. The test result stratifies patients into low, medium, or high-risk for complicated disease progression over time. As such, this test may provide a useful tool for estimating prognosis in pediatric CD patients, when considered together with clinical factors, including older age at diagnosis and presence of perianal

disease or deep ulcers on colonoscopy, which have also been associated with stricturing/ internal penetrating behavior. The implication is that earlier use of immune modulator or anti-TNF therapy may reduce the rate of progression in these high risk patients; however, that has not yet been conclusively established. A prospective cohort study of 796 pediatric CD patients using a novel system dynamics analysis of clinical outcomes and AMS suggested that early use of immune modulators or anti-TNF therapy would reduce the risk of complications in high risk patients [39•]. Importantly, this project also developed a patient decision aid that can be used in the office to review an individual patient's risk factors and the potential effect of specific therapies. However, as AMS titers vary with age within the pediatric age range, it will be important to validate this model in younger children enrolled in RISK. Once that has been accomplished, it is quite likely that this will become a useful clinical tool.

Therapeutic Targets for Improving Linear Growth and Body Composition

Linear growth failure and reduced lean mass and bone density are important complications of pediatric CD. Recent registry studies have shown that deficits in growth persist even in the age of steroid-sparing immune modulator and biologic therapy. We conducted a prospective cohort study to examine, in a cohort of incident CD patients, the relationship between changes in inflammatory cytokines and growth factors, and linear growth and body composition [40]. We found that while overall lean mass improved with therapy, there was variation across the cohort. The greatest increase in lean mass was experienced by patients who received infliximab, had the greatest increases in serum albumin, and had the greatest decreases in the inflammatory markers erythrocyte sedimentation rate and IL-6. Consistent with prior cohorts, overall height z scores did not improve during a median of 43 months of follow-up. However, catch-up growth, or improvement in height z score, was associated with greater increases in insulin-like growth factor 1, and greater decreases in the inflammatory factors TNF α and IL-6. Therefore, monitoring of these inflammatory and anabolic markers may be helpful in assessing whether a specific therapy is likely to promote linear growth and increased lean mass.

Predicting Response to Therapy

There is great interest in developing genetic and immune models to predict response to therapies in addition to providing prognostic information. Because of the cost and risk associated with biologic therapies for IBD, as more of them become available, the utility of tools to guide selection will become even greater. Two pediatric studies in the past year have utilized genomic approaches to predict the response to corticosteroid and infliximab therapy, respectively [41, 42]. In the first, the global pattern of gene expression in PBMC obtained on day 3 of intravenous corticosteroids for 128 children with severe UC was determined. A panel of 10 genes differentially expressed between corticosteroid responders and non-responders classified these groups with 80% sensitivity and specificity. If validated in a future study, this gene panel could be used, in conjunction with clinical parameters including the Pediatric Ulcerative Colitis Activity Index, to select patients for earlier use of infliximab. In the second study, genetic polymorphisms identified using genome-wide association studies were used to develop a model to predict response to infliximab in 94 pediatric

subjects with CD or UC. Overall, 22 did not respond. A model that included four genetic polymorphisms, UC diagnosis, and pANCA seropositivity was highly accurate in predicting lack of response to infliximab (area under the curve for the receiver operator curve of 0.98). It should be possible to validate this model for primary non-response to infliximab within the RISK cohort. If validated, this may become a useful tool to help assess the risk/benefit ratio of infliximab therapy.

Conclusions

Data from large prospective registry studies have recently led to revision of the clinical phenotyping guidelines for children with IBD. This new approach, termed the Paris Classification system, accounts for VEO (< age 10) and EO (age 10-17) age of onset, and recognizes the unique features of extensive small bowel disease with the L4b modifier. It will be important to utilize this system when designing and reporting results from future translational studies, outcomes registries, and clinical trials. A tremendous amount of new information regarding the specific etiology of infantile forms of IBD has become available over the past two years. Much as has occurred for neonatal cholestasis, this new information has broadened the differential diagnosis and specific evaluation of these patients (see Table 1). Importantly, if a single immune gene mutation is identified in a particular patient, this may support the use of allogeneic stem cell transplantation. A large body of literature now supports the use of prognostic panels including the *NOD2* genotype, AMS, and pANCA in estimating risk for progression to stricturing or penetrating behavior in CD (see Table 2). While validation of a model which includes the effects of early age of onset and specific therapies offered early in the disease course is eagerly awaited from RISK, it would be reasonable to include the commercially available Crohn's Prognostic Panel in current clinical care. It is important to note that the frequency of AMS titers may differ in children younger than 10 years old compared to older patients, and so the currently available models may not be applicable to these youngest patients. While recent studies to develop predictive models for induction therapies are more preliminary, it is anticipated that as these models are validated in large prospective cohort studies, and hopefully in clinical trials, they will enter clinical practice as well.

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Table 1

Pathogenesis and Diagnostic Tests for Infantile Enterocolitis

Disorder	Presumed IBD Pathogenesis	Screening Test
Common Variable Immune Deficiency	Defective cellular and/or humoral immunity	Lymphocyte subsets, IgA, IgM, IgG, IgE, vaccine titers
CGD	Defective phagocyte microbial killing	Neutrophil oxidative burst
Dyskeratosis Congenita	Premature telomere shortening leading to stem cell dysfunction	Telomere length in PBMC
IPEX Syndrome	Defective regulatory T cell function	FOXP3 expression by flow cytometry
IL10R Mutations	Defective IL-10 anti-inflammatory action	IL-10 signaling in PBMC (research assay)
Wiskott-Aldrich Syndrome	Effector & regulatory lymphocyte defects	WASP expression by flow cytometry
XIAP deficiency	Combined microbial response and regulatory T cell defects	XIAP expression by flow cytometry

Table 2

Genetic and Serologic Predictors of Disease Behavior

Predictor	Associated Disease Behavior
<i>NOD2</i> genotype	Ileal CD location & stricturing behavior. Increases risk of stricturing for each level of anti-microbial serology (AMS).
ASCA	Stricturing and internal penetrating behavior. Lower titers in CD < age 10 at onset.
pANCA	Colon-only CD location & reduced risk of stricturing behavior.
CBir1	Stricturing and penetrating behavior. Relatively higher titers in CD < age 10 at onset.
GM-CSF Ab	Ileal CD location & stricturing behavior. Increasing titers with increasing age of onset.
I2	Stricturing & penetrating behavior.
OmpC	Stricturing & penetrating behavior.