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NASPGHAN Single Topic Symposium: Discovering the Future of Pediatric IBD Care

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Despite the advent of biologic therapy and other recent advancements in our understanding of pediatric inflammatory bowel disease (IBD), rates of clinical relapse, poor quality of life, psychosocial dysfunction, hospitalization and surgery remain unacceptably high. Pediatric IBD, affecting between 71 and 212 of every 100,000 children(1) is thought to be particularly aggressive, resulting in frequent hospitalization, surgery and psychosocial dysfunction.(2,3) Despite the frequent use of immunomodulators(4–6) and anti-tumor necrosis factor (anti-TNF α) agents,(7) there has been limited improvement in outcomes over the last several decades.(8) Optimizing outcomes for children and adolescents with IBD or other chronic illnesses requires a multi-faceted research and QI agenda that includes basic science, clinical efficacy, clinical effectiveness, comparative effectiveness, health services research, and QI. (9) As there are relatively small numbers of patients at any given center, highly coordinated collaborative efforts are required to determine which interventions are most promising, and how those interventions can most reliably be delivered. However, rarely do professional societies, foundations, government agencies and patients and their families work together to establish and implement an integrated research agenda.

One reason for the slow improvement in outcomes is widespread variation in the management of IBD due to a lack of consensus on best management practices and inadequate care delivery systems.(10) Inappropriate variation in pediatric (and adult) IBD care has been well documented, with studies showing inadequate dosing of medications, failure to screen for potential complications according to established guidelines, and inconsistent use of effective therapies.(10,11) Recent research suggests that QI interventions can decrease variation in care and improve outcomes,(12) however significant room for improvement remains.

Dougherty and Conway(9) proposed a model to organize research efforts, transform health care delivery and improve outcomes. In their model, 3 major translational steps (T1, T2 and T3) would occur, with each step progressively building on and broadening the findings in prior steps. Specifically, therapies discovered through traditional basic biomedical science would undergo evaluation to determine clinical *efficacy* (T1). Therapies that showed efficacy in well-defined populations would be subject to outcomes, comparative effectiveness, and health services research to determine whether they showed *effectiveness* in broader populations (T2). Clinically effective therapies could then be studied to determine how best to implement, scale and spread them in clinical practice, how to increase the reliability of providing such therapies, and the value associated with each (T3). Achieving the best possible outcomes for patients would only be achieved by maximizing efforts at each translational step.

Implementing such a model requires significant cooperation among interested stakeholders, including patients, researchers, clinicians, improvement specialists, regulators and governmental and foundational funding agencies. In order to accomplish this critical step “**Discovering the Future of Pediatric IBD Care**” was held October 17th, 2012 in Salt Lake City. Invited speakers included members of NASPGHAN, the Crohn’s and Colitis Foundation of America (CCFA), the Food and Drug Administration (FDA) the National Institutes of Health (NIH), and patient and parent representatives. The organizing committee was comprised of Wallace Crandall (Chair), Bob Baldassano, Athos Bousvaros, Ted Denson, Neera Gupta and Laura Mackner.

Objectives

The overall objectives of the symposium were to bring together stakeholders to review state of the art research and therapy in pediatric IBD, and to explore and define a combined research and quality agenda for the next 5 years that will result in improved outcomes for these patients. Specific aims of this symposium included:

1. Bring together basic, translational, clinical and QI pediatric IBD researchers and clinicians to share their work and consider areas of synergistic collaboration
2. Inform the wider community of pediatric gastroenterologists of existing research in pediatric IBD, particularly regarding currently funded research
3. Provide support, networking, and potential collaboration to young investigators interested in pediatric IBD
4. Communicate current state of the art medical therapy in pediatric IBD
5. Define, prioritize and widely communicate a future research and QI agenda for pediatric IBD

Specific Program

It is not feasible to review all current pediatric IBD research in a single symposium. We therefore organized the meeting around 5 topics that share 3 common traits. First, each topic has clear clinical implications for improving IBD care. Second, modules were generally based on currently funded research. Finally, topics were selected so that each area of translational research described by Dougherty and Conway was represented to allow researchers and clinicians to begin to envision an integrated research and quality agenda.

The symposium was primarily comprised of five modules examining risk stratification, QI and health care delivery, emerging concepts in pathogenesis, future medical therapy and research priorities for the next 5 years. Modules typically included a “State of the Art”

review, lectures on current research, recommendations for future research related to the topic of that module, and a question and answer period to maximize communication between participants and presenters. The symposium concluded with a presentation summarizing the research priorities for the next 5 years, determined by the program speakers, moderators and organizing committee and the recently published CCFA research agenda.(13)

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Risk Stratification

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Risk stratification for specific outcomes at diagnosis or during the early course of disease may help improve prognostic information provided to families, determine optimal medication strategies to decrease rates of specific complications in high risk patients, determine optimal surveillance strategies in those patients at greatest risk, improve overall disease course, improve our understanding of determinants of disease behavior over time, and optimize study designs. To date, we have been imperfect and often wrong in our ability to predict disease course and rationally design new therapeutic interventions.

Early intervention with therapies that have the potential to alter the natural history of disease and slow down or prevent disease progression is important. While immunomodulator and biological therapy decrease corticosteroid dependence and can improve clinical outcome and quality of life in children with Crohn's disease, their use is not without increased risk of infection and possibly neoplasia. Risk stratification of children most likely to develop complicated disease requiring more intensive therapy at the time of diagnosis using immune, genetic, and microbial markers and phenotypic attributes will provide both clinicians and parents a better model in which to assess risk-benefit ratio of current and emerging therapies.

The currently accepted etiopathogenic hypothesis for IBD proposes that the interaction of host genetics, specifically "pre-programmed" host immune responses and environmental factors such as enteric flora, result in disease susceptibility, development, and eventual expression.⁽¹⁾ These factors and their interactions may also be important determinants of disease phenotype and disease progression.

Over 160 IBD susceptibility genes have been confirmed in genome wide association studies. Understanding the significance of these genes is an important task. Many of the genes appear to be aligning in functionally relevant pathways.^(2,3) For example, following gene discoveries in autophagy and innate immunity, defective processing of intracellular bacteria became a central theme in Crohn's disease. In addition, the importance of barrier function to the development of ulcerative colitis has been supported by genetic evidence. These pathways are significant because they reveal the importance of interactions between the host and the enteric microbiota in maintaining intestinal homeostasis and provide insight into the pathogenesis of IBD. The enteric microbiota is an important "environmental factor" in IBD.^(4–6) The environment influences the onset and phenotype of IBD via alterations in the microbiota as well as the host immune response.^(1, 7–8)

Childhood-onset IBD, Crohn's disease in particular, may be an indicator of increased genetic predisposition to develop disease, but, due to other factors, may not always lead to

the most severe clinical course (i.e. an aggressive or complicated clinical course as seen in the 15% of patients who require surgery within 3 years of diagnosis).(9) Studies have shown that in pediatric patients with Crohn's disease, complicated disease behavior increases with time and is a risk factor for surgery.(10–12) Female sex and older age at diagnosis are risk factors for complicated disease and surgery.(12–14) Female sex and older age at diagnosis decrease the risk for growth impairment.(15–20) Extensive disease and increasing disease severity increase the risk for post-operative disease recurrence.(21,22) Most recently, 1500 treatment naive children from 28 centers across North America with newly diagnosed IBD were recruited into a large prospective cohort study sponsored by the Crohn's and Colitis Foundation of American. DNA, serology, and microbiota were obtained to develop prediction models of risk for complicated disease. Initial findings support that identifiable and unique genetic, serologic, and microbial risk factors for complicated disease can be found at the time of diagnosis. In addition "high risk clusters" have been identified within the study population. Development of tool sets to understand disease mechanisms, predict events, and discover and optimize individual therapeutic intervention strategies is under way.(23)

Moving forward, to address the dire unmet medical need for predictive biomarkers of disease course,(24) response to therapies,(25–27) adverse events to therapeutic interventions, and to efficiently identify new therapeutic targets that work in the majority of patients, we must learn from past miscalculations and apply new knowledge to treat and cure IBD. It is important to acknowledge that the current state of the art is rapidly evolving, as many strongly held concepts have been proven to be incorrect. Further research in pediatric patients with Crohn's disease is needed to clarify risk factors for specific outcomes, understand the underlying mechanisms for increased risk, enhance treatment regimens based on individual patient risk, and optimize surveillance strategies.

Quality Improvement and Health Care Delivery

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Much of medical research focuses on "what should be done", with little attention paid to "how" to reliably accomplish it. In fact, the reliable implementation of therapeutic plans is extremely poor, with only 60% of desired care being delivered to the patient.(1–3) ImproveCareNow, a pediatric IBD QI network, is using theory driven QI efforts to reduce this unintended variation in care. These efforts include attempts to standardize evidence based care guidelines, the use of the Model for Improvement to rapidly test and implement successful interventions, and serial "Learning Sessions" where centers meet to share successful strategies. Underlying and providing structure to these efforts is Wagoner's Chronic Care Model (4) which emphasizes the domains of self-management support, delivery system design, decision support and clinical information systems.

Achieving the best possible outcomes for patients requires a spectrum of research and QI efforts across multiple areas of "translation" as described above. We typically think of this process of translational research as moving from "bench" to drug discovery and then to randomized controlled trials to establish therapeutic efficacy. While critical, there is also an

increasing focus on equally important, yet “non-traditional,” translational research. One example is the topic of self-management and adherence. Adherence to prescribed treatment in chronic illness generally, and pediatric IBD specifically is poor, with adolescents missing up to half of their oral medication doses.⁽⁵⁾ Poor adherence to therapy may be influenced by a number of factors related to the individual, community and the health system, and successful interventions to improve self-management behavior must take these factors into consideration. A group based intervention to improve adherence in pediatric IBD has shown limited success,⁽⁶⁾ demonstrating the complexity of factors influencing adherence. An individualized intervention was more successful; however issues of scalability and convenience must also be addressed.⁽⁷⁾ Ongoing research is examining a telemedicine approach to individualized interventions, with plans to examine not only the response to the intervention, but also which components are most important and what patient factors predict response to different interventions.

Additional non-traditional areas of translational research include the use of medical technology, meaningful use of electronic health records, comparative effectiveness research and system redesign. Pediatric IBD has become central to much of this research, serving as a model for improving outcomes not only in IBD, but in chronic disease generally. ImproveCareNow is working with investigators from the Collaborative Chronic Care Network (C3N) and Enhanced Registries (ER) grants to re-design chronic illness care in pediatric IBD. The C3N project is focusing on building leadership and community around chronic illnesses, and is bringing together multiple stakeholders including patients, families, clinicians, researchers, improvement specialists, communication and media experts, information technology and computer science authorities and others to accomplish this goal. This allows for the distribution of discovery and implementation of better ways to care for patients across large groups of like-minded, engaged stakeholders, thereby increasing the rate of innovation and improvement. C3N has been instrumental in developing a number of tools to help facilitate improved care. Examples of these tools include a patient self-management handbook, technology driven patient activation tools, “N of 1” trials (single patient experiments to optimize care), passive tracking of patients health status, peer and parent mentoring programs, and disease-related online communities.

The ER project aims to develop a system where “research grade” clinical data can be collected at the point of care and then used for both QI and comparative effectiveness research. These researchers are working with vendors of electronic medical records (EMR) to establish templates for standardized data collection that are part of each patient’s EMR. These data are, in part, downloaded to a central database that then generates automatic reports returned to the participating sites. These include “pre-visit planning” reports that compare the patient’s current treatment (e.g. drug dosing) to established “model care guidelines” and report patient specific outcome measures (e.g. remission and growth status) with suggested considerations where indicated. These reports are used to plan each patient’s next clinic visit. Sites also receive population management reports that identify all of the patients in a given practice who fall within certain categories (e.g. patients on corticosteroids, patients not seen in the last 6 months, patients not in remission) so that they can be targeted for additional interventions between clinic visits. These reports also stratify patients by a combination of clinical factors that may place them at higher risk (e.g. active disease and/or recurrently active disease, treatment with corticosteroids, compromise of growth and/or nutrition status, psychosocial dysfunction, etc.) and therefore may be deserving of more careful clinical attention.

The same data used for QI are being re-purposed for comparative effectiveness research. For example, using the ImproveCareNow database, researchers have recently performed a “real-world” recapitulation of the REACH trial, a prospective study of infliximab in children with

Crohn's disease, as well as a trial comparing anti-TNF use with other treatment strategies, both at a fraction of the cost of the corresponding clinical trials.

Collecting data at the point of care and effectively using it for both research and QI is central to the development of a "Learning Health System," a concept put forth by the Institute of Medicine in 2006. A Learning Health System should "generate and apply the best evidence for the collaborative choices of each patient and provider; to drive the process of discovery as a natural outgrowth of patient care; and to ensure innovation, quality, safety, and value in health care" (see Figure 1). The Learning Health System envisions a "Learning Engine" that occurs at the point of care. Clinical data would be collected through EMRs from patients, their families and clinicians at each clinic visit, and that data would be fed back to providers for QI purposes to improve outcomes. The same data would be used for comparative effectiveness research, and would be analyzed to identify gaps in care and uncertain management practices which could be targeted for further research and QI efforts. ImproveCareNow, C3N and ER investigators are working together to develop a pediatric IBD Learning Health System.

Emerging Concepts in Pathogenesis and Therapy

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Dysbiosis in Inflammatory Bowel Disease: Cause or Effect?

Studies using germ free (GF) mice have shown that the enteric flora are required for the development of experimental IBD and, by extension, human disease.(1) Interestingly, the pattern of neonatal bacterial colonization has been shown to differ between normal and colitis-prone mice, suggesting that genetic variation in the host may influence early colonization, development of the mucosal immune system, and the later emergence of clinically apparent IBD.(2) Moreover, intriguing animal studies have shown that mono-association of genetically susceptible IL-10 deficient mice with different bacterial strains will lead to disease in discrete segments of the small intestine or colon.(2) These findings in mice have suggested that antigens derived from the enteric flora could drive the development of IBD in humans. In this regard, several recent studies have identified differences in bacterial colonization of the gut in IBD patients.(3) 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*.(3–5) 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.(6) *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.(4,6) 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. (7) It will be important in future studies to account for genetic and acquired differences in host innate immunity which may promote dysbiosis, and to begin define whether sustained modification of the flora will exert a beneficial effect in specific individuals.

Pathogenesis of Very Early Onset Inflammatory Bowel Disease

Infantile and very early onset IBD (VEO-IBD), diseases that occur in children younger than 10 years of age, are severe and sometimes fatal. The incidence of these debilitating forms of intestinal inflammation has soared over the past decade and now comprises 25% of all pediatric IBD.(8) Young children develop a disease whose clinical features and natural history differ significantly from the IBD commonly observed in older children and adults. IBD diagnosed in very young children frequently fails to respond to traditional therapies used in older children and adults.(9) In addition to the early age of onset and distinctive clinical features, VEO-IBD patients are more likely to have familial disease.(9) That makes this a particularly fruitful group in which to identify susceptibility genes that play a leading role in the pathogenesis of these specific forms of disease. However, no major genetic studies have been carried out in VEO-IBD patients. Recent studies suggest that specific variants in immunodeficiency genes (e.g., IL-10R, CGD pathway) that are known to have colitis as part of their clinical spectrum are associated with VEO-IBD.(10,11) Based on these observations, VEO-IBD patients may have unique genetic variants and environmental triggers and these genes may play a more important role in the disease pathogenesis in young children than in older children and adult-onset IBD. A unique subset of VEO-IBD patients are diagnosed before age one. These “infantile” IBD patients make up an estimated 1% of pediatric IBD. In this group, the likelihood is highest (of all VEO-IBD patients) of identifying single-gene variants responsible for colitis. Finally, due to developmental differences, various environmental influences—for examples, the effects of the microbiome and nutrition—may play critical roles in IBD pathogenesis that are unique to children. Studying IBD through the lens of VEO-IBD will likely increase understanding of the cause of IBD in older children and adults, and shed light on the normal mechanisms of intestinal immunity. In this regard, the international Early Onset IBD Cohort Study (NEOPICS; www.NEOPICS.org), a network that includes numerous sites in North American and international medical centers, has partnered together with numerous other cohorts in the US and internationally to focus on the etiology of VEO-IBD.

Cell-Based Therapies in Inflammatory Bowel Disease: Regulatory Cells to Mesenchymal Stem Cells, are They a Viable Option?

Crohn’s disease is mediated by an inflammatory cytokine cascade that includes IL-12, IL-23, IFN γ and IL-17.(12) The mucosal immune system down modulates inflammation through innate suppressor cells called T regulatory cells. These cells secrete suppressive cytokines such as IL-10 and TGF- β , which can down modulate the aforementioned inflammatory cascades.(12) These T regulatory cells have “plasticity” and can change the nature of their function from suppressive to inflammatory pending the microenvironment present (i.e. inflammatory cytokines).(13) Present treatment for Crohn’s disease patients include a multitude of therapies directed at these inflammatory pathways. In cases of medically non-responsive patients bone marrow transplantations have been performed with long-term remission.(14) These treatments however, are not without risk and the mechanism of response has not been fully explored. Additional approaches to address these immune abnormalities in IBD patients can include other modalities of “stem” cell therapy. Mesenchymal stromal cell (MSC) are stromal cells derived from various sources, which include the bone marrow or adipose tissue.(15) These MSC cells are also “plastic” in nature and can respond to inflammation by altering the type of microenvironment present, through the activity of inflammatory cells present or through suppressive cytokines such as IL-10 and/or TGF- β .(16) Clinical trials in adult patients are currently testing the utility of this approach.(17)

Clinical Implications of Current Pathogenic Concepts

Recent translational studies have provided new insights into pathogenesis, disease behavior, and treatment responses in pediatric IBD. 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.(18) 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.(19) Therefore, it will be important to validate these models in the younger age groups. To address the need to validate genetic and serologic models of disease behavior in the pediatric age group, and potentially improve these through measurement of cytokine auto-antibodies and tissue microbial and host gene expression patterns, the RISK study, a prospective inception cohort study sponsored by the Crohns and Colitis Foundation of America (CCFA), has now enrolled 1500 pediatric IBD patients at 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.(18) 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.

The Future of Medical Therapy

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Historically, goals in treating pediatric IBD were to control symptoms, while facilitating normal linear growth and development. Chronic intestinal inflammation commonly persists, particularly in Crohn's disease, despite resolution of clinical symptoms, and such chronic uncontrolled inflammatory disease progresses to penetrating and structuring complications. Given ways of better monitoring intestinal inflammation and more effective therapies, treatment goals have therefore altered to include intestinal healing, aiming to improve long-term outcomes. Data concerning the efficacy of medical treatments in achieving mucosal and, in Crohn's disease, transmural healing are relatively limited and have been accrued predominantly in adult populations. Limited pediatric data suggest that exclusive enteral nutrition is associated with mucosal healing more often than corticosteroids in Crohn's disease, despite comparable efficacy in achieving clinical remission.(1) The adult SONIC trial was a prospective randomized control trial comparing the efficacy and safety of monotherapy with azathioprine, monotherapy with Infliximab and combination therapy with azathioprine and infliximab. This adult study provided prospective, but disappointing data concerning the ability of azathioprine to achieve resolution of intestinal lesions. Anti-TNF and combination therapy are more effective; early use is important in optimizing healing in Crohn's disease.(2) Implementation of intestinal healing as a therapeutic goal is intuitively satisfying. Challenges in the real world of clinical practice include treatment resistance of sub-types of IBD, uncertainty concerning the degree of persistent intestinal inflammatory disease that may be appropriate to accept, lack of reliable predictors of aggressive progression versus indolent disease, and concerns about safety and durability of long-term immunomodulatory and biologic treatments.

To help answer these important issues we will need to develop investigator initiated trials. The fundamental processes required for an individual investigator to initiate a clinical trial are well established; there are many practical obstacles that an inquisitive clinician must conquer in order to implement their research plan. In recent years, a number of well-organized clinical research networks have been established within the North American Pediatric IBD community. Each has an underlying infrastructure that facilitates the Network's main research objective. A variety of network models are available to independent clinical researchers to efficiently address unique and novel questions. The success of such endeavors depends on the researcher recognizing the constraints of the available resources within the network and conceptualizing study questions that are answerable within such boundaries. Researchers have already utilized existing datasets to answer new questions and are beginning to access existing organizations to facilitate new independent trials. Arguably, however, the ultimate power of utilizing existing infrastructure is to have them simultaneously inform and recruit for future trials.

Efficacy endpoint and clinical outcome assessment are key to the development of a successful pediatric clinical trial. The choice of which outcome assessment to use in a clinical trial depends upon the concept that one seeks to measure (i.e., the specific goal of the measure) as well as the intended *context of use*. Context of use is as a complete and precise statement of what circumstances are appropriate for use of the Clinical Outcome Assessment (COA) and how it is applied in the drug development and approval process. Patient reported outcome (PRO) measures are required for the assessment of a symptom, which is defined as any subjective indicator of a disease, health condition, or treatment-related effect that the patient is aware of and that is known only by the patient. A PRO is any measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's response.

The pediatric community must work together to develop pediatric clinical trial which will direct future pediatric IBD therapy. Inflammatory Bowel Diseases are characterized by chronic intestinal inflammation involving a pathological response in both the innate and adaptive immune systems. This is the result of genetic susceptibility, environment, immune system dysfunction and commensal enteric flora. To date our therapeutic approach has been to target the excessive activity of the adaptive immune system. Future therapies will enhance the innate immune system and block the infiltration of inflammatory cells into the intestinal mucosa. New therapies will include either biological agents or small molecules. Biologic therapies are high cost, very selective, excellent potency, and limited off-target toxicity but have high immunogenicity and long half life. Small molecules have no immunogenicity, are less expensive and are given orally. Overall, much progress has been made in understanding the pathogenesis of IBD, and many potentially useful treatments are under development, but few are available. In the pipeline are several drugs which appear to be effective.⁽³⁾ For example, anti-adhesion molecules such as vedolizumab are being developed to selectively block the integrin $\alpha 4\beta 7$. This selective blocking hopefully will decrease the possibility of significant side effects seen with other anti-integrin drugs. A similar safety profile should occur with anti-MAdCAM-1 or anti-recombinant $\beta 7$ antibodies. Another molecule is ustekinumab, which is an antibody against IL-12/IL-23. A phase II trial showed this drug to be effective for the treatment of Crohn's disease, and phase III trials are ongoing. A small molecule, tofacitinib, an inhibitor of Janus kinase 3 is being studied for the treatment of ulcerative colitis and Crohn's disease.⁽³⁾

Future IBD therapies will require a more targeted patient-based approach that makes use of genetic information and biomarkers to deliver tailor-made therapy.

The Road Ahead: Priority Areas for Future Research and Quality Improvement Work

Jill Plevinski, MA

Steve McPhail

Athos Bousvaros, MD

The closing session of the “Discovering the Future of Pediatric IBD Care” symposium highlighted different perspectives (patient, parent, and physician), focusing on how IBD health care can be improved in the future. Ultimately, the development of medical and technological innovations in health care has five goals:

1. To allow the development of less invasive tests that will facilitate diagnostic testing.
2. To allow health care providers to predict who is at risk of developing complications of the disease, and thus needs stronger therapy (risk stratification).
3. To develop reliable ways of monitoring disease activity (surrogate markers).
4. To develop more effective and less toxic therapies.
5. To identify ways of preventing the disease in patients at risk (e.g. children and siblings of index cases).

In her talk, Jill Plevinsky, an IBD patient that is currently a research assistant at Boston Children’s Hospital, emphasized that successful biomedical research requires an active partnership between health care provider and patient. In this mutual relationship, both groups are “givers and takers”. The physician “gives” his biomedical knowledge, expertise, and compassion to the patient, while the patient gives their personal experiences, history, and individual perspective to the physician. In addition, physical “goods” are exchanged: the physician prescribes medication, while the patient provides clinical samples for patient care. If both groups decide to work together on research projects, informed consent and mutual collaboration are even more essential. The essential components of this collaboration are empathy, trust, and a shared goal to improve the health of children with IBD.

Steven McPhail, the Chief Executive Officer of Expression Analysis and a member of the board of the Improve Care Now Network, spoke on the benefits of QI initiatives. He proposed the dissemination of “evidence based” medicine (i.e. medical practice based on published literature) as opposed to “eminence based” medicine (medical practice based on the clinical patterns of senior physicians). QI collaboratives have the opportunity to compare outcomes among different centers, identify what practices lead to improved patient health, and disseminate these innovations more efficiently throughout the improvement network. The end result is an overall increased remission rate in centers in the collaborative.

Athos Bousvaros, pediatric IBD specialist and the current NASPGHAN president closed the symposium by highlighting what progress has been made and what still needs to be done. While research in both genetics and the microbiome has progressed rapidly, the application of these novel technologies to clinical practice remains in its infancy. In addition, there remains a paucity of clinical trials in pediatric IBD. For example, aside from the Markowitz trial randomizing children with CD to mercaptopurine or placebo, there are no randomized trials evaluating treatment of new onset pediatric CD. (1) Further comparative studies (for example comparing mercaptopurine to methotrexate in new onset pediatric CD) are necessary to provide benefit/risk information to physicians and parents.

The research and quality agenda (See Appendix 1) highlights important areas of need for the next 5 years. The agenda was developed by the organizing committee, with the input of IBD experts and the broader NASPGHAN membership. Specifically, the committee compiled suggested priority items from themselves, meeting moderators and speakers, other individuals considered experts in IBD and from a draft of the now published CCFA “Challenges in IBD research: Update on progress and prioritization of the CCFA’s research agenda.”(2) The organizing committee met by teleconference to discuss and prioritize the suggested agenda items and prepared an initial agenda. This research and quality agenda was presented at the single topic symposium, and meeting participants were asked to provide feedback. Following the meeting, the agenda was finalized and is presented below.

This agenda proposes research in a number of areas, including genetics, the microbiome, environmental factors, growth and development, psychological assessment, adherence, clinical trials, and QI. Those with an interest in pediatric IBD research are encouraged to read this document, the CCFA Challenges manuscript and prior documents highlighting research needs in IBD (2,3). The collaborative groups formed by pediatric IBD specialists (including the PROKIIDS and Improve Care Now Networks), will, over the next decade, work fervently to address these gaps in knowledge, and to improve the well-being of children with this serious chronic illness.

Appendix 1

Proposed Combined Research and QI Agenda, 2013

Define clinically relevant subsets of IBD patients using genetic, immunologic, microbial, tissue expression, and clinical profiles (including drug levels) that will predict aggressiveness of disease, complications and response to treatment.

Examples:

1. Develop a model of prognostic factors in pediatric IBD that is reliable and clinically relevant.
2. Define distinct sub-types of Crohn’s disease and ulcerative colitis, and determine which therapeutic approaches are most safe and efficacious for each sub-type.
3. Understand the racial/ethnic differences in presentation, development of complications, and response to treatment
4. Define the natural history of very early onset IBD

Understand how environmental factors enhance the risk of IBD through effects on microbial, epigenetic, immunologic, and mucosal barrier influences.

Examples:

1. A specific focus upon the role of diet is warranted.

Determine which environmental triggers initiate, perpetuate, and/or reactivate disease.

Examples:

1. Determine the role of psychosocial stressors, antibiotic exposure, infection, vitamin D and other postulated factors that may affect disease activity.

Further understand reciprocal interactions (cross-talk) between genes, microbiota, epithelial cells, and innate and adaptive immune responses that determine pathways mediating homeostasis versus inflammation.

Examples:

1. Determine critical rate-limiting cell/cellular pathways for communication with the microbiota.
2. Define critical cell types and pathways in relevant cell lines leading to further understanding of homeostasis versus inflammation, with an ultimate goal of putative (therapeutic) targets.

Determine optimal treatment approaches and strategies through comparative effectiveness studies.

Examples:

1. Determine the effectiveness and safety of therapeutics in pediatric IBD. This would include not only specific therapies, but also therapeutic paradigms such as rapid step up vs. top down therapy.
2. Develop RCTs in pediatric IBD (e.g. withdrawal of dual therapy)
3. Understanding pediatric dosing and pK of biologics

Develop improved tools for measuring disease activity in IBD.

Examples:

1. Develop inexpensive, non-invasive biomarkers of disease activity that can accurately predict disease relapse and define the degree of disease activity.
2. Determine the feasibility and utility of mucosal healing as a primary outcome measure.

Improve our understanding of underlying mechanisms of growth impairment and delayed puberty

Maximize the effectiveness of QI techniques for discovering and implementing methods to improve outcomes in pediatric IBD

Examples:

1. Understand the role of contextual factors in determining success in quality improvement efforts as manifest by improved patient outcomes.
2. Understand the most effective means of scaling and spreading effective quality improvement interventions, including issues of financial sustainability that would allow broad participation.
3. Determine which QI interventions (Population Management, Pre-Visit Planning, Self-management, etc.) have the greatest impact in improving outcomes, including factorial design strategies and the importance of sequencing interventions.
4. Develop a sustainable model to integrate research and QI into a learning health system
5. Determine how to rapidly and reliably identify and implement assessment and treatment recommendations as they are developed.
6. Determine how to measure health system performance
7. Examine the role of on-line engagement in facilitating patient activation

Define the role of improved self-management and psychosocial functioning on outcomes in pediatric IBD

Examples:

1. Examine the roles of stress, coping and social support on self-management and outcomes, and determine which components and interventions have the greatest impact on outcomes. Interventions could include social networking, in-person mentoring, use of technology, surveillance of functional status, etc.
2. Examine the effect of childhood onset IBD on school functioning and early employment and educational pursuits.
3. Understand what factors influence successful transition of care, how they can be assessed, and what interventions are most effective in improving the transition process.
4. Understand the factors that influence effective self-management, including adherence, how they can be measured, and what interventions are most effective in improving self-management.
5. Test novel approaches to facilitating changes in health behaviors. Such approaches might include “real time healthcare” using passive patient reported outcomes, N of 1 trials, disease specific social networking, etc.

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graph LR; PF[Patients and Families] --> POC((Point of Care  
The Learning Engine)); C[Clinicians] --> POC; POC --> SPP[Standardize Process  
Reduce Variability in Process  
Customize Process to Patient Needs]; SPP --> PO[Patient Outcomes]; PO --> IAG[Identify New Gaps in Care]; IAG --> RA[Registry Applications]; RA <--> RD[Registry Database]; RD --> CER[Comparative Effectiveness Research]; CER --> IUP[Identify Uncertain Management Practices]; IUP --> POC; RD -- New Knowledge --> POC; RD --> EHR[Electronic Health Records]; EHR --> POC; EHR --> IUP; RD --> DNR[Distributed Network of Registries]; DNR --> RA; DNR --> RD;
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The diagram illustrates the Learning Health System (LHS) model, showing the flow of information and the iterative cycle of learning and improvement. The central component is the **Point of Care** (The Learning Engine), which receives input from **Patients and Families** and **Clinicians**. The Point of Care leads to **Standardize Process** (Reduce Variability in Process, Customize Process to Patient Needs), which then leads to **Patient Outcomes**. From Patient Outcomes, the process moves to **Identify New Gaps in Care**, which feeds into **Registry Applications** and **Registry Database**. The Registry Database and Registry Applications are connected by a bidirectional arrow. The Registry Database feeds into **Comparative Effectiveness Research**, which leads to **Identify Uncertain Management Practices**. This box then feeds back into the Point of Care. The Registry Database also feeds back into the Point of Care, labeled as **New Knowledge**. The Registry Database and Registry Applications are connected to a **Distributed Network of Registries**, which feeds back into the Registry Applications. The Registry Database also feeds into **Electronic Health Records**, which feeds back into the Point of Care. The Registry Database also feeds into **Identify Uncertain Management Practices**.

Figure 1.
The Learning Health Care System