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Evaluation of pediatric acute ulcerative colitis management protocol

Samantha Simons

Evaluation of Pediatric Acute Ulcerative Colitis Management Protocol

by

Samantha Simons

Thesis

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MASTER OF SCIENCE

in

Clinical Research Administration

Thesis Committee:

Jean Rowan, MD, MS, Chair

Haley Neef, MD

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Ypsilanti, Michigan

Abstract

Pediatric patients with ulcerative colitis (UC) represent a high-risk population with severe disease that requires hospitalization. This study evaluates the impact of implementing an acute UC management protocol on 39 pediatric patients. After analysis, significant trends were shown for admitted pediatric patients post-protocol implementation, helping to coordinate multi-disciplinary care sooner during a hospital stay. The patients were more likely to have a surgical consult, and the surgical consult was completed closer upon admission. The median length of hospital stay did not change, total parenteral nutrition use was increased, and oral steroids upon discharge were decreased. Anti-tumor necrosis factor alpha was given to more patients earlier upon admission, and the colectomy rate did not change but was more likely to be conducted sooner as an inpatient procedure. While further research with a larger patient population is needed, the benefits of an acute UC management protocol have been shown.

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Introduction

Inflammatory bowel disease (IBD) is a term used to describe disorders that involve chronic inflammation of the digestive tract. The two main forms of IBD include Crohn's disease and ulcerative colitis (UC). Although these two diseases share some characteristics, they can be differentiated by specific clinical, endoscopic, and specialized histological features (Ordás, Eckmann, Talamini, Baumgart & Sandborn, 2012). UC is confined to the colon, and inflammation is generally limited to the mucosal surface. Crohn's disease can cause inflammation in any part of the gastrointestinal (GI) tract and penetrate the deeper layers of the tissue (Baumgart & Sandborn, 2012).

Currently, there is no cure for IBD. Treatment is centered around management of symptoms and prevention of complications, with the goal of remission. Targets for remission include resolution of clinical symptoms, defined as recovery of rectal bleeding with positive changes in bowel habits, and endoscopic healing (Ungaro, Mehandru, Allen, Peyrin-Biroulet & Colombel, 2019). Patients with UC may reach and maintain remission with oral medications (Higgins, 2010). Sulfasalazine and aminosalicylates (mesalamine, olsalazine, and balsalazide), are usually first-line treatment with an expected remission rate of about 50% (Danese & Fiocchi, 2011). Although aminosalicylates are the main choice of treatment for mild to moderate UC (Nielson & Munck, 2007), approximately 15% of patients with UC will have subsequent relapses or flares that can turn into a severe exacerbation (Doherty & Cheifetz, 2009). Corticosteroids, such as oral prednisone are the first-line treatment used to treat flares (Carter et al., 2004). Intravenous (IV) steroids, immunosuppressants and biological drugs such as monoclonal antibodies or tumor necrosis factor (TNF) inhibitors are often used in moderate to severe exacerbation of the disease (Lis, Kuzawińska & Bałkowiec-Iskra, 2014).

Severe exacerbation of UC symptoms or acute UC may constitute a medical emergency requiring hospitalization. Patients hospitalized for acute UC benefit from a multidisciplinary team comprising of a gastroenterologist and a colorectal surgeon (Kedia, Ahuja & Tandon, 2014).

Since pediatric patients hospitalized with acute UC require a rapid multidisciplinary approach including coordination of medical, surgical, and nutritional interventions, an acute UC management protocol was created. A protocol is a standard set of rules or procedures to be conducted and followed in formal situations, which allow many individuals to communicate efficiently with each other. The goal of our acute UC management protocol was to standardize and improve care, ensuring that all rotating caregivers at an academic medical center follow the same implemented clinical management protocol for any patient hospitalized for UC exacerbation. This protocol was created by pediatric gastroenterologists and surgeons with expertise in IBD and initiated in November 2014. To assess the efficacy of the protocol, medical, surgical, and nutritional interventions in hospitalized pediatric patients were measured before and after implementation of the management protocol.

The development of the project flowchart system (Appendix A), clearly defines steps and processes to apply to the care of a patient admitted with a UC flare. This protocol begins with all acute UC patients being admitted to the GI floor of the hospital. The protocol requires the gastroenterologist to document the Pediatric Ulcerative Colitis Activity Index (PUCAI) score on a daily basis. The PUCAI is a validated and frequently used primary outcome measure to reflect disease activity in pediatric UC (Turner et al., 2009). The protocol includes an initial assessment with surgeons upon admission, to involve surgeons early on in case medical management fails, and to introduce the possibility of a colectomy to the family to improve their knowledge and

understanding of surgical intervention should it need to happen during the admission. A colectomy is a surgical procedure to remove all or part of the colon. A colectomy may be considered on any day in the management of acute UC patients if medical management does not produce the desired outcomes and may be required emergently if patient develops intestinal perforation, exsanguinating hemorrhage or toxic megacolon (Macken & Blaker, 2015). If by hospital Day 5 a patient's PUCAI score is greater than 65, this predicts a need for greater escalation of therapy or surgery. Patients who fail treatment or who do not respond to therapy within 72 hours will require a colectomy per the acute UC protocol. The involvement of surgeons at the time of admission is critical. In children, 10% of acute UC patients undergo a colectomy prior to discharge, with a cumulative colectomy rate at 1 year of 20% (Rosen, 2015). Although most patients will respond to medical therapies, a colectomy can be lifesaving for some patients (Maken & Blaker, 2015).

The acute UC management protocol also requires a nutrition evaluation at the time of admission. The Nutrition Evaluation (Appendix B) begins with access to STRONGkids to determine individual caloric needs. STRONGkids is a nutritional screening tool for hospitalized children, established to predict a negative weight for height standard deviation score in a lengthy hospital stay (Huysentruyt et al., 2013). Hypoalbuminemia in UC is predominately due to protein loss from severe colitis, not from malnutrition (Hendrickson, 2002). If albumin levels are below 2.0 g/dL, the physician should consider IV albumin supplementation and begin total parenteral nutrition (TPN), even if enteral nutrition is preferred. It is often preferred over parenteral nutrition, since it is associated with significantly fewer complications than parenteral nutrition in acute colitis (Seres, Valcarcel & Guillaume, 2013). Nutrition consultations are important to establish acute and chronic nutritional needs, to identify if a patient is not meeting oral caloric

needs, and to assist the physician in a decision about whether tube feedings and/or parenteral nutrition is needed. This will also allow for planning for the placement of a peripherally inserted central catheter (PICC). Since these patients are prone to malnutrition and its detrimental effects (Burke, Lichtenstein, & Rombeau, 1997), it is important to address any nutritional issues early on during admission so that the patient has the best chance of recovering during and after hospitalization for acute UC.

At admission, the protocol advises initial medical management with IV steroids for 48 hours as well as appropriate nutritional support. The response to steroids is indicated by improvement in patients' symptoms (decreased stool frequency, urgency and rectal bleeding, improved stool consistency, minimized abdominal pain, and improvement in general wellbeing utilizing the PUCAI score) and improved lab parameters. Due to potential side effects, there is a need to limit the overall duration of corticosteroid use for flares, and physicians need to institute a corticosteroid-sparing agent whenever possible for long-term disease maintenance (Feuerstein et al., 2019). After 3 days, a PUCAI score greater than 45 predicts likely failure to the first line of treatment, steroids. Anti-TNF therapy can be used in acute steroid-resistant UC patients who prefer to avoid surgical management if possible (Gibson et al., 2015). If family opts for anti-TNF, the protocol advises starting infliximab at 10 mg/kg. This dose is commonly used in to treat pediatric UC (Nattiv et al., 2012). Acute UC patients benefit from this dose for induction into remission (Turner et al., 2012).

The objective of this study was to evaluate and measure the involvement of physicians, surgeons, and registered dietician services during a pediatric acute UC admission before and after protocol implementation. Data regarding patients acute UC hospitalization was collected, and data was extracted to assess clinical outcomes.

We hypothesized that the implementation of a standardized pediatric acute UC protocol would show significant effect on the timing of nutrition and surgical evaluation when a patient is admitted to the GI service for acute UC flare. We were also interested in evaluating the effect of the acute UC protocol on overall length of admission, the timing and frequency of colectomy, and the timing and outcomes of medical intervention implemented, per protocol, in a standardized fashion (anti-TNFα, TPN, steroids). Preliminary study findings were previously published as an American Gastroenterological Association (AGA) abstract (Milewski et al., 2016).

Methods

This study was reviewed by both the University Human Subjects Review Committee (UHSRC) at Eastern Michigan University (2018), and the Medical School Institutional Review Board (IRBMED) of the University of Michigan Medical School (2015; see Appendices C and D). Both IRBs ruled that this was not considered human subject research and did not require IRB approval since it does not satisfy the definition for human subject research under federal regulation 45 of the Code of Federal Regulations (CFR) section 46.102.

Data was collected using retrospective chart review of the electronic medical record and stored with a numeric identifier to remove protected health information (PHI). After IRB review for this study, data for every pediatric patient hospitalized for acute UC exacerbation and as an acute UC flare was then captured in chronological order from January 2013 up to the protocol implementation date on November 1, 2014. In addition, the succeeding patients admitted with acute UC characteristics after the management protocol implementation date were identified by physicians during weekly meetings until January 2016 and collected into the same database.

The following data was extracted from each hospitalization record: admission date/discharge date, nutrition consult ordered/completed, surgery consult ordered/completed, initiation of TPN, whether patient had a colectomy and when, and if the patient was discharged on oral steroids. This would allow a review to see if there was a difference in outcomes before and after management protocol implementation.

Analysis

Data collected for the study was retrieved from the electronic medical record (EMR) and placed into a password protected Excel worksheet. Data from pre-protocol and post-protocol implementation were grouped for analysis. Statistical descriptive analyses were conducted by

using Pearson's chi-square, and Fisher's exact test to evaluate the data and investigate differences between the groups. The p-value used for all tests of significance was $p = .05$.

Results

There were a total of 39 patients admitted for acute UC exacerbation included in this study (Table 1). Table 1 shows patient demographics. Twenty of these patients were reviewed pre-protocol (from January 2013 to November 2014), and 19 patients collected post-protocol implementation (November 2014 to January 2016).

Table 1.
Acute UC Protocol Management —Patient Demographics

Description		Frequency All Patients	Frequency Before Protocol	Frequency After Protocol
Age	0-9	6	4	2
	10-15	22	9	13
	16-20	11	7	4
Gender	Male	21	12	9
	Female	18	8	10
Diagnosed prior to admission	Yes	38	19	19
	No	1	1	0
Exposure to anti-TNF before admission	Yes	10	2	8
	No	29	18	11
On oral steroids prior to admission	Yes	11	7	4
	No	28	13	15

The length of admission was recorded for all acute UC patients for both before and after implementation of the acute UC management protocol is shown in Figure 1. Before protocol implementation, there were a total of 20 acute UC hospitalizations that ranged from 3 to 18 days in length (mean 7.4 days), with 6.5 days as the median length of stay. After protocol implementation, there were 19 consecutive hospitalizations that ranged from 3-53 days in length (mean 15.9 days; $p = .02$), with a median of 6 days, represented by a dashed line ($p = .73$).

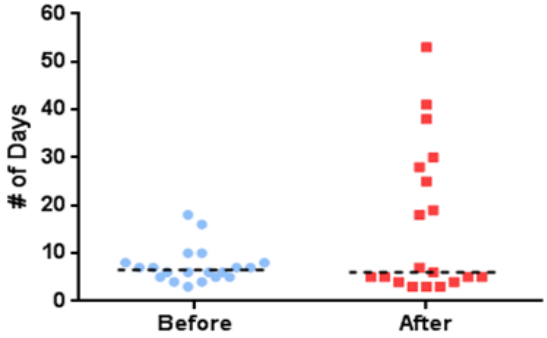


Figure 1. Length of hospitalization.

Whether or not a registered dietician's nutrition evaluation was completed, along with the average day of hospitalization that the consult was completed, is shown in Figure 2. The frequency of nutrition consults being completed before and after protocol implementation were both 95% (p = 1). There was no significant difference on the average day the nutrition consult was completed during hospital stay (3.1 vs. 2.5 days, p = .25).

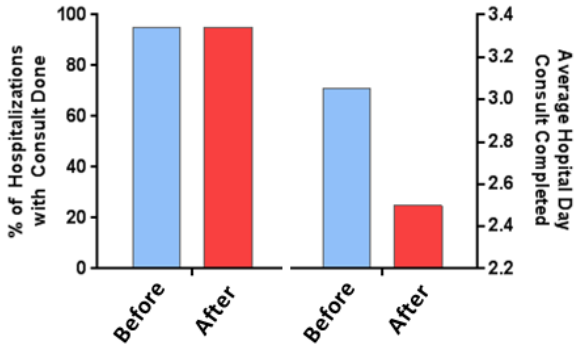
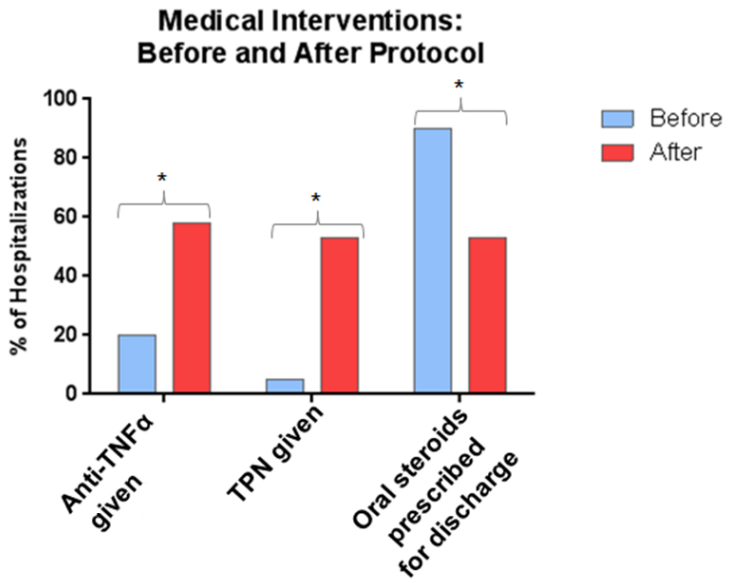


Figure 2. Nutrition evaluation and consultations.

Three medical interventions were recorded during the acute UC admission as shown in Figure 3. The first intervention studied was whether or not the patient received an anti-TNF alpha inhibitor therapy medication. Before the protocol was implemented, only 20% of patients received this medication (on average hospital Day 9), and after the protocol, 58% of patients received anti-TNF during admission (p = .02) (on average hospital day 4.3; p = .02).

TPN was the second medical intervention studied. Prior to the protocol implementation, only 5% of patients studied received intravenous nutrition, whereas 53% of patients received TPN after protocol implementation (p = .001). The third medical intervention shown in Figure 3 is whether or not acute UC patient were discharged on oral steroids. Prior to the protocol, 90% of patients were discharged on oral steroids, and after the protocol, only 53% were discharged on oral steroids (p = .01).



*= $p \leq .05$

Figure 3. Medical interventions.

Figure 4 shows the percentage of surgical consultations completed, along with the average day the surgical consult was completed. Before protocol implementation only 15% of patients had a surgical consult ordered, but after protocol implementation, 79% of patients had a surgical consult ordered (p = .0002). The average hospital day that the surgical consultation was completed prior to protocol implementation was on Day 10.7. After protocol implementation, the surgical consult was completed 7.1 days sooner, on average Day 3.6 (p = .04).

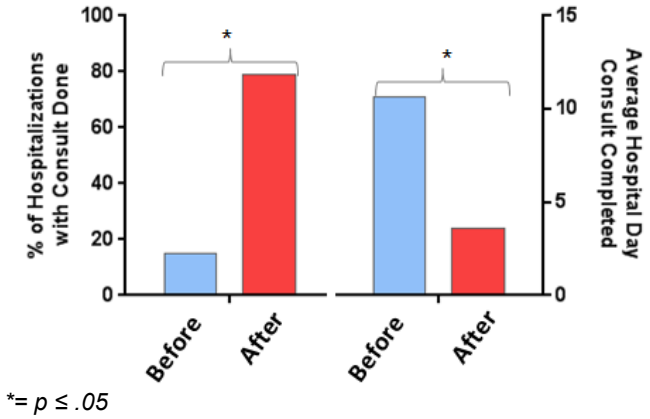


Figure 4. Surgical consultation completed.

Figure 5 shows a total of 16 of the 39 (41%) acute UC patients underwent an inpatient or scheduled outpatient colectomy following hospitalization(s) for acute UC flare(s), 7 out of 20 (35%) patients before management protocol implementation (indicated by a dashed line), and 9 out of 19 (47%) patients received colectomies after protocol implementation. The two patients who had an initial admission before the protocol implementation but were discharged after are included in the after group, since they had subsequent readmissions after protocol implementation. The average day patients underwent colectomy was significantly sooner (p = .02) after protocol implementation (mean = 64.1 days) than those with initial admission for flare prior to the protocol (mean = 225.9 days).

Figure 5 also shows 14% (1 patient) of the colectomy patients underwent the surgery during their admission (inpatient colectomy) before the management protocol was introduced, indicated by red square in Figure 5. After implementation of the protocol, 66% (6 patients) received the surgery as inpatients (p = .04).

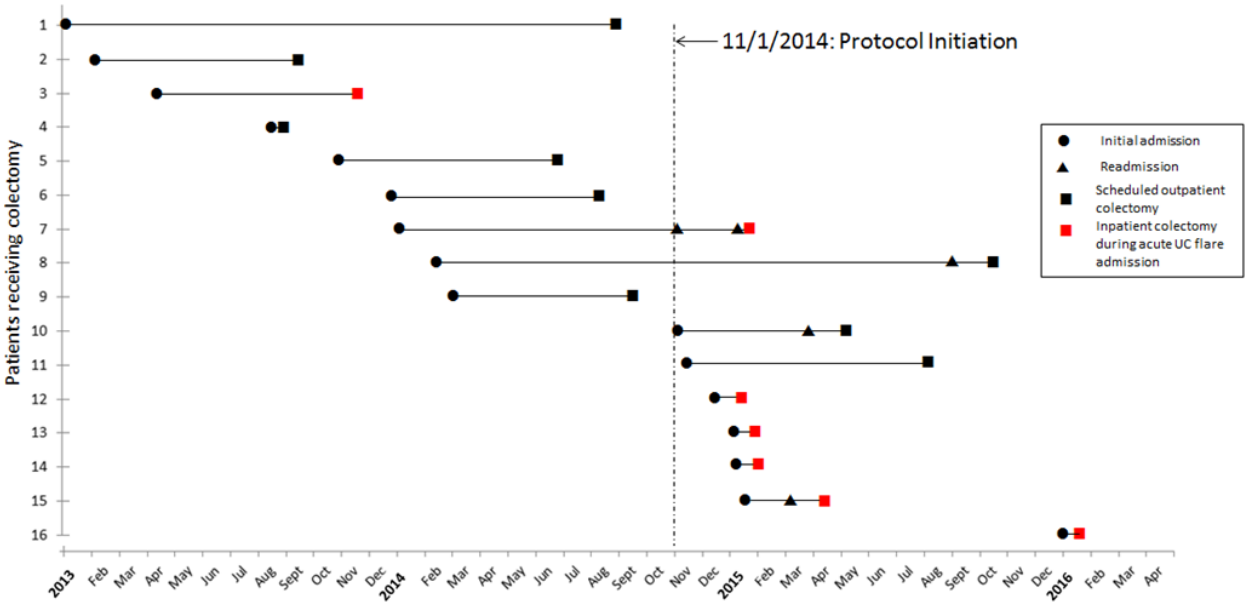


Figure 5. Timing from initial acute UC admission to colectomy.

Table 2 summarizes the location of the patients who underwent a colectomy. Either during initial hospitalization for flare, during a hospitalization following a re-admission for flare, or as a scheduled surgical procedure after discharge- due to failure of outpatient medical management after previous hospitalization(s) for flare(s).

Table 2.
Patients Colectomy Service: Summary of location/service when colectomy was performed

Description	Total Colectomies	
	Before Protocol	After Protocol
Inpatient–initial hospitalization	1	4
Inpatient–re-admission	0	2
Outpatient–scheduled procedure	6	3

Discussion

The purpose of this study was to evaluate the implementation of an acute UC management protocol and identify the effect on the frequency and timing of the evaluation by surgeons and dieticians, the duration of hospitalization stay, the frequency of medical intervention use (anti-TNFα, TPN, steroids), and the occurrence of colectomy due to treatment failure. The results were obtained from pediatric patients being admitted at an academic medical center for acute UC (n = 39) from January 2013 to January 2016. They were collected both before (n = 20) and after (n = 19) acute UC management protocol implementation on November 1, 2014.

The review of length of stay revealed there was a significant increase in the mean length of hospitalization (7.4 vs. 15.9 days, p = .02). This was possibly prolonged secondary to post-operative complications. The median length of hospitalization was not significantly different (6 vs. 6.5 days, p = .7).

Regarding the involvement of nutritional intervention, the nutrition evaluation completed by a registered dietician was completed with the same rate of frequency (95% vs 95%, p = 1). Nutrition consults were completed on average 0.6 days sooner after protocol implementation, but this was not significantly different (3.1 vs. 2.5 days, p = .25).

In regard to medical interventions, after protocol implementation, more patients were given anti-TNF alpha inhibitor therapy (20% vs 58%, p = .02) and given on average 4.7 days sooner (9 vs. 4.3 days; p = .02) after the management protocol was instituted. After protocol initiation, significantly more patients received TPN (5% vs. 53%, p = .001) during their hospital stay, and lastly, significantly fewer patients were discharged on oral steroids (90% vs. 53%, p = .01). We hypothesize that patients subjected to the acute UC management protocol were assessed

more closely and objectively for response to steroids and that they were thus less likely to be discharged on unnecessary steroids, possibly sparing them negative side effects of this drug category. Perhaps just implementing a management protocol influences care-providers, actions by prescribing more TNP and more anti TNFα, which could lead to less patients being discharged on oral steroids.

The involvement of surgeons completing a surgical consult increased significantly after protocol implementation (15% vs. 79%, $p = .0002$). These surgical evaluations were also completed sooner (Day 10.7 vs. Day 3.6, $p = .04$) during hospitalization. Although there appeared to be an improvement on the surgical consult being completed sooner, the t-test showed it was not statistically significant ($p = .18$), possibly due to the fact that surgical consult was only ordered for three patients prior to the protocol and for 13 patients after the protocol.

The majority of acute UC patients did not undergo a colectomy ($n = 23$; 59%). The protocol implementation did not significantly increase the rate of undergoing colectomy during stay, possibly due to small sample size ($n = 16$), with a relatively small number of hospitalizations after the protocol that were possibly prolonged secondary to post-operative complications. The total number of patients undergoing a colectomy during admission ($n = 7$) decreased after protocol implementation, although there was not a significant difference ($p = .06$). This trend demonstrates that if a patient will ultimately need a colectomy, they are being done more often in-patient after protocol implementation. The earlier and more frequent surgical consults may have led to more inpatient colectomies, which could of ultimately lead to less discharge on steroids. Since this analysis was done with a such small sample size, a p-value of > 0.05 only signifies that the evidence is not adequate to reject the null hypothesis. This does not imply that the two treatments are equivalent.

Inconsistency in care sometimes encountered at an academic hospital for complex, sick patients such as those admitted with acute UC symptoms is problematic. First, families may hear conflicting information from various caregivers, leading to confusion and a lack of trust in the medical system. Second, it is impossible to tell whether a care pathway provides the best outcomes for a patient if it is not being used consistently and appropriately. Third, necessary care may be delayed if a multidisciplinary approach is not taken early on during a hospital stay. Implementation and evaluation of an acute UC management protocol allowed us to identify and understand these problems through data measures. Continuing to educate rotating staff is essential to supporting ongoing, correct use of the protocol to continue to study outcomes. We would benefit from ongoing use of this protocol with data collection so that clinical outcomes can be more closely studied on a larger population basis.

Conclusions

An evaluation of the effect of implementing an acute UC management protocol was completed on 39 pediatric acute UC hospitalizations. After analysis, significant trends where shown for admitted pediatric patients post management protocol implementation helping to coordinate multi-disciplinary care sooner during a hospital stay. Although the median length of hospital stay did not change, anti-TNFα was given earlier and to more patients. The patients were more likely to have a surgical consult, and the surgical consult was closer to admission. More patients received TPN, and fewer patients were discharged on oral steroids. The patients' nutritional consults during hospitalization continued to be early upon admission for both pre- and post-protocol implementation. The overall colectomy rate did not change but was more likely to be conducted sooner and as an inpatient procedure. Additional research is warranted, but with the statistically significant outcomes gathered from this small study, the meaning for practice going forward will hopefully spare patients of negative side effects of steroids and continue to involve all rotating caregivers in the patients plan of care. While further research with a larger patient population is needed, the benefits of an acute UC management protocol have been shown.

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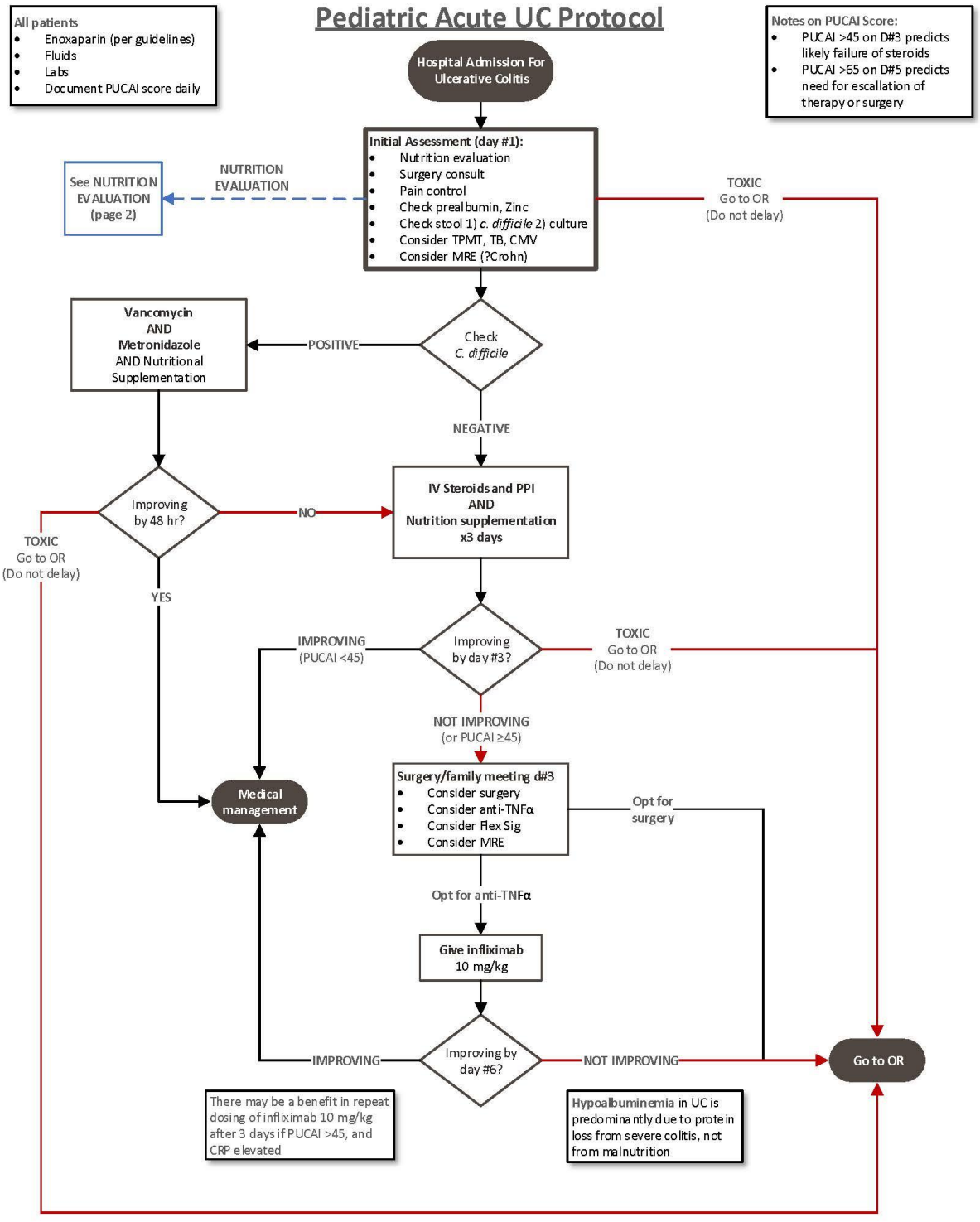
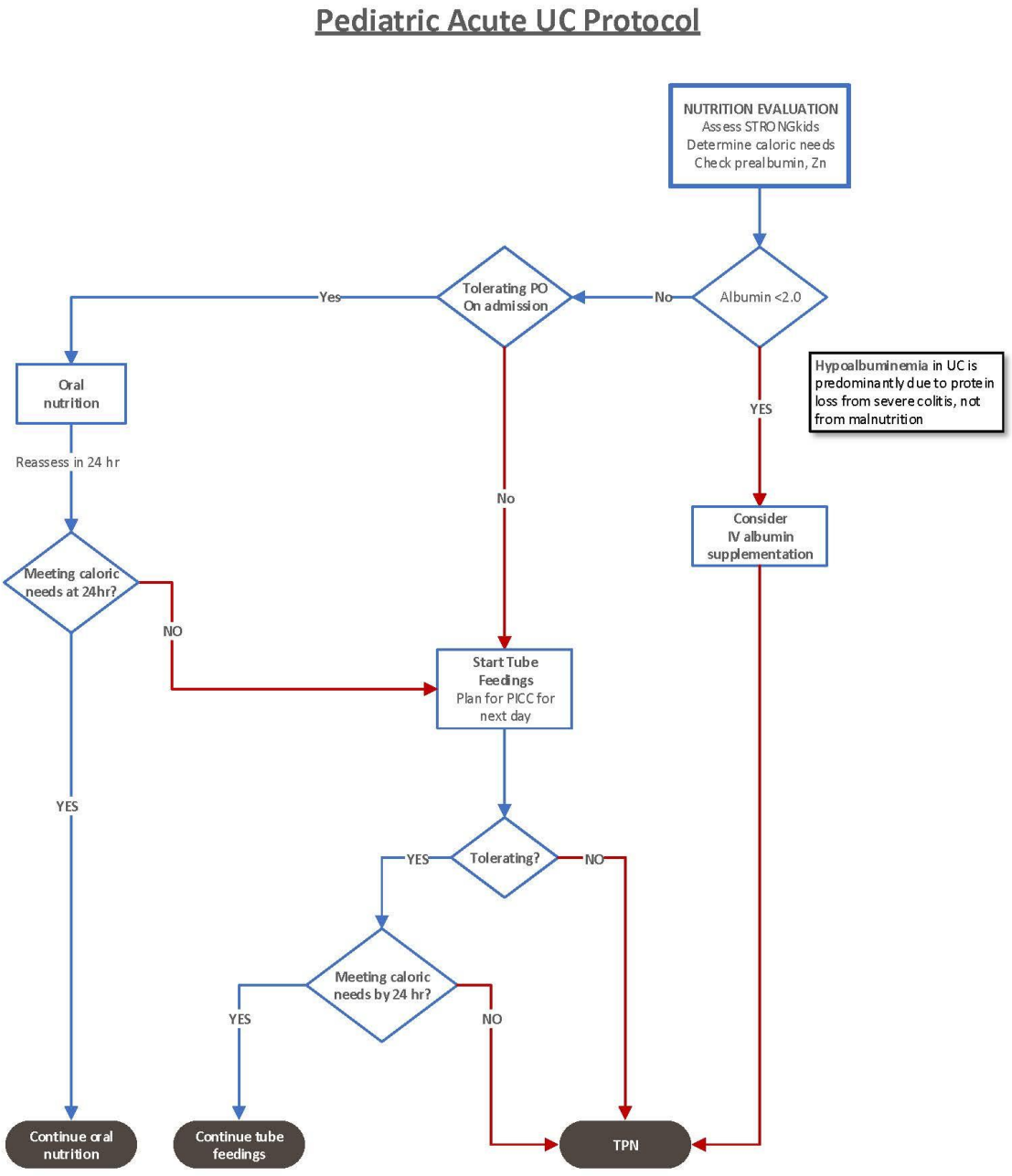
APPENDICES

Appendix A: Acute UC Protocol



Appendix B: Acute UC Protocol-Nutrition Evaluation



Appendix C: Response Letter from EMU Human Subject Review Committee

Jan 12, 2018 2:41 PM EST

Samantha Milewski
Eastern Michigan University, School of Health Sciences

Re: Initial - UHSRC-FY17-18-222 Evaluation of Pediatric Acute Ulcerative Colitis Protocol

Dear Dr. Samantha Milewski:

The Eastern Michigan University Human Subjects Review Committee has rendered the decision below for Evaluation of Pediatric Acute Ulcerative Colitis Protocol.

Decision: No Human Subjects Research

Findings: Your project does not require UHSRC review in accordance with federal regulation 45 CFR 46.102 because it does not meet the Federal definition of human subject research. UHSRC policy states that you, as the Principal Investigator, are responsible for protecting the rights and welfare of your research subjects and conducting your study as described in your protocol.

Please contact human.subjects@emich.edu with any questions or concerns.

Sincerely,
Eastern Michigan University Human Subjects Review Committee

Appendix D: Response Letter from UofM Human Subject Review Committee

Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road, Building 520, Suite 3214, Ann Arbor, MI 48109-2800
phone (734) 763 4768 • fax (734) 763 9603 • irbmed@umich.edu

Subject: Notice of Determination of "Not Regulated" Status for [HUM00105220]

SUBMISSION INFORMATION: Title: Evaluation of pediatric acute ulcerative colitis protocol Full Study Title (if applicable): Evaluation of an inpatient protocol for management of acute ulcerative colitis exacerbation in pediatric patients Study

eResearch ID: HUM00105220
Date of this Notification from IRB: 10/9/2015
Date of IRB Not Regulated Determination: 10/9/2015

IRB NOT REGULATED STATUS:
The IRBMED has reviewed the application referenced above and determined that, as currently described, it does not require IRB approval because it does not satisfy the definition research under 45 CFR 46.102(d), 21 CFR 56.102(c), or U-M policy as described in Human Research Protection Program Operations Manual Part 4. Research is defined as "…a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."
The purpose of this Quality Assurance/Quality Improvement (QA/QI) initiative is limited to
Improving healthcare quality and/or delivery; and/or Collecting, measuring, and/or reporting patient or provider data for clinical, practical, training or administrative purposes
In accordance with OHRP FAQ on this subject (see http://www.hhs.gov/ohrp/policy/faq/quality-improvement-activities/improve-quality-of-patient-care.html and http://www.hhs.gov/ohrp/policy/faq/quality-improvement-activities/measuring-reporting-provider-performance-data.html) there is no requirement for such activities to undergo review by an IRB, or for these activities to be conducted with provider or patient informed consent.

NOTE: QA/QI initiatives sometimes also constitute non-exempt human subjects research under the HHS regulations: these require IRB review and approval. See OHRP FAQ at http://www.hhs.gov/ohrp/policy/faq/quality-improvement-activities/types-of-quality-improvement-efforts.html and http://www.hhs.gov/ohrp/policy/faq/quality-improvement-activities/need-to-be-reviewed.html

Any proposed changes that may introduce a research component, or may exceed the approval conditions of any other non-IRB reviewing committees, must be submitted as an amendment through eResearch.

DATA SECURITY GUIDELINES AND CONFIDENTIALITY PROTECTIONS:
You are responsible for maintaining data for the QA/QI initiative in a secure manner with the appropriate level of anonymity, confidentiality, or de-identification as a key factor in ensuring a low risk threshold for the participants and the University. The IRB recommends you follow the U-M "Core data security controls" outlined at http://research-compliance.umich.edu/data-security-guidelines. Also, consult the Sensitive Data Guide to IT Services at http://safecomputing.umich.edu/dataguide/ in deciding where to safely store and share sensitive data using U-M IT services.

HIPAA PRIVACY RULE COMPLIANCE:

UMHS Privacy Board has not reviewed this project. HIPAA Privacy Rule permits a covered entity to use and disclose protected health information for quality-related health care operations activity. Per 45CFR164.502(a)(1):

(1) Permitted uses and disclosures. A covered entity is permitted to use or disclose protected health information as follows:

(ii) For treatment, payment, or health care operations, as permitted by and in compliance with § 164.506;

The definition at 45CFR164.501 specifies:

Health care operations means any of the following activities of the covered entity to the extent that the activities are related to covered functions:

(1) Conducting quality assessment and improvement activities, including outcomes evaluation and development of clinical guidelines, provided that the obtaining of generalizable knowledge is not the primary purpose of any studies resulting from such activities; …

(2) Reviewing the competence or qualifications of health care professionals, evaluating practitioner and provider performance, health plan performance, conducting training programs in which students, trainees, or practitioners in areas of health care learn under supervision to practice or improve their skills as health care providers, training of non-health care professionals, accreditation, certification, licensing, or credentialing activities;

SUBMITTING AMENDMENTS VIA eRESEARCH: You can access the online forms for amendments in the eResearch workspace for this not regulated project, referenced above. Note that no Amendment is required by IRBMED except when the design or aims of the project are changing such that the "Not Regulated" determination may no longer be appropriate.

ACCESSING NOT REGULATED PROJECTS IN eRESEARCH: Click the "Exempt and Not Regulated" tab in your eResearch home workspace to access this not regulated project.

Michael Geisser Co-chair, IRBMED
Alan Sugar Co-chair, IRBMED