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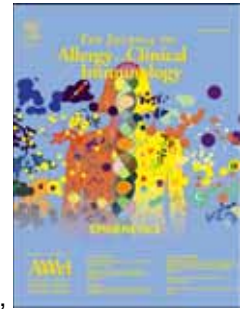
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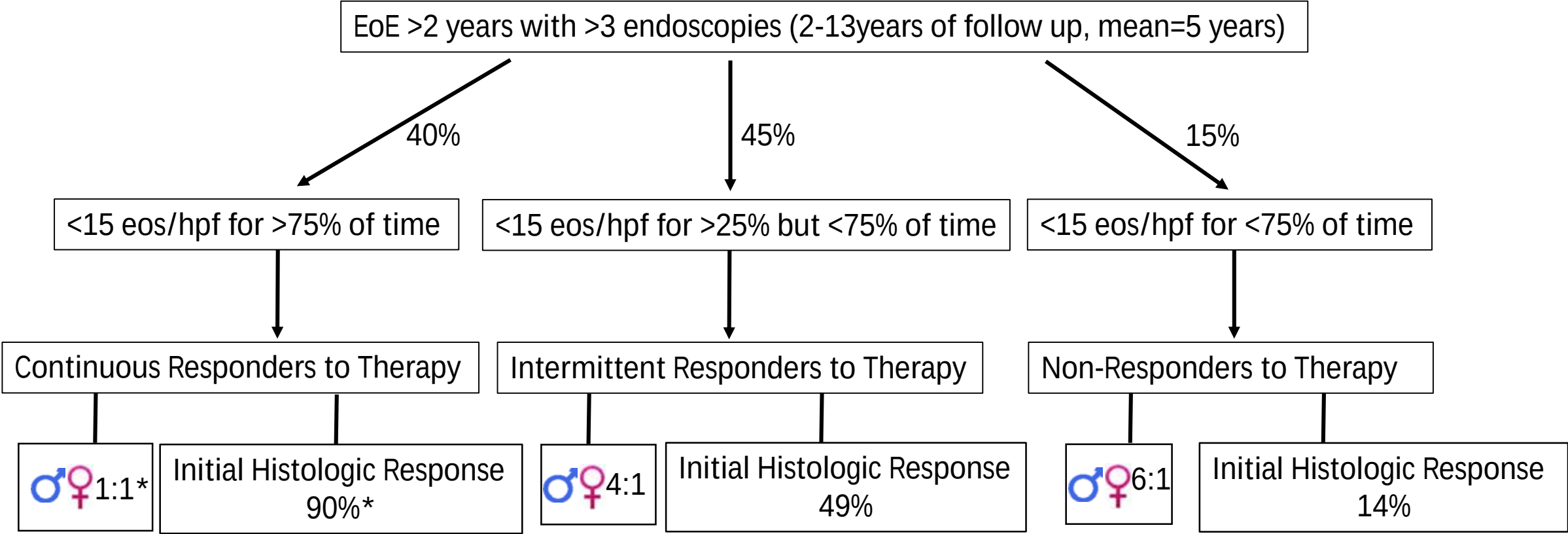
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*p<0.001 between groups
hpf: high power field

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Distinct Histologic Patterns and Clinical Characteristics

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Abstract

Background: Eosinophilic esophagitis (EoE) is a chronic, increasingly prevalent antigen driven disease. There is a paucity of information on long-term course in children.

Objective: To understand the longitudinal trajectory of pediatric EoE during routine clinical care.

Methods: We prospectively enrolled children into an EoE database and reviewed their medical and pathology records over 13 years.

Results: From 2011 to 2015, 146 EoE children seen for their first visit at our center had ≥ 2 years of follow up and ≥ 3 endoscopies over an average follow up time of 5.13 years (range 2-13). Longitudinal eosinophilic inflammation during treatment demonstrated 3 patterns over time. Children with < 15 eosinophils per high power field (hpf) for $> 75\%$ of their follow up time were termed “continuous responders” (CR). Children with waxing and waning inflammation of < 15 eosinophils per hpf for $< 75\%$ but $\geq 25\%$ of follow up time were termed “intermittent responders” (IR). “Non- responders” (NR) were defined as < 15 eosinophils per hpf for $< 25\%$ of their follow up. 59 of 146 (40%) patients were CR; 65 of 146 (45%) were IR; 22 of 146 (15%) were NR. CR patients differed from IR and NR patients on the parameters of male to female ratio (1:1 in CR, 4:1 in IR, 6:1 in NR) ($p < .001$) and in their initial response to any therapy, including PPI ($p < .001$). Endoscopic severity correlated with esophageal eosinophilia ($r = 0.73$, $p < .001$). On multivariate analysis, female sex and initial therapeutic response to medications or elimination diet associated with long-term control of esophageal eosinophilia.

Conclusions: Long-term pediatric EoE followed 3 different longitudinal trajectories of inflammation. The long-term histologic groups differed significantly in biological sex and initial therapeutic response.

Clinical Implication: Female sex and initial therapeutic response may be predictors of favorable longitudinal outcomes in pediatric EoE.

Capsule Summary. We have defined 3 distinct longitudinal courses of EoE that associate with sex and initial therapeutic response.

Key words. Therapy response, Eosinophil, Eosinophilic Gastrointestinal Disorder, Pediatric, Elimination diet, Topical corticosteroid, Longitudinal

Abbreviations.

CR- Continuous Responder

hpf- High power field

IR- Intermittent Responder

NR- Non-Responder

PPI- Proton Pump Inhibitor

SPT- Skin prick test

Introduction

Though the diagnosis of eosinophilic esophagitis (EoE) has become more common, the clinical features that predict longitudinal trajectories during therapy in children remain enigmatic. These issues are paramount for guiding clinical decisions in a chronic disease that requires repeated invasive monitoring for diagnosis and management. EoE is a Th2 antigen driven clinicopathologic diagnosis with symptoms of esophageal dysfunction such as vomiting, dysphagia, and pain and an eosinophil predominant inflammation of ≥ 15 per high powered field (hpf).^{1, 2} Currently the estimated prevalence is 0.5-1 cases/1000 persons and is increasing, creating a growing healthcare burden.³

Despite many advances in understanding EoE, prognostic data for therapy response and progression to complications is lacking, especially in children. Thus, there is little data to guide personalized treatment decisions such as optimal therapeutic interventions and the time intervals between endoscopies. Until the most recent update to the EoE diagnostic guidelines, standard medical management started with a proton pump inhibitor (PPI) trial. However, given the clinical and molecular similarities between PPI-resistant and responsive patients, PPIs are now considered an EoE directed therapy.⁴ Beyond PPIs, EoE management consists of either topical corticosteroids, elimination diets, or both. Surgical management with dilation is reserved for patients with critical strictures.²

Generally, EoE is considered a chronic disease with a very low spontaneous remission rates.⁵⁻⁸ Studies in adults have found high relapse rates in terms of symptoms when therapy is discontinued, although there are no randomized trials of

longer-term therapy beyond a few months and no large-scale systematic longitudinal assessment of eosinophilic inflammation to correlate with symptoms. Patients can have histologic EoE relapse while on therapy, often due to reductions or changes in the regimen of topical corticosteroid use.^{5, 9-12} Despite incomplete control of eosinophilia, EoE-directed therapies such as topical corticosteroids can improve the rate of complications such as food impactions.¹³⁻¹⁵ Currently, the mechanisms behind disease relapse and loss of response to therapy are unclear.

In this study, we report the results of a prospectively enrolled pediatric EoE cohort followed for 2-13 years. We identified sub-groups with distinct patterns of eosinophilic inflammation over time. Distinguishing these differences in longitudinal disease course allowed us to evaluate the demographic and clinical parameters by histologic inflammatory patterns over time. These data could help to inform the identifying clinical features that associate with longitudinally persistent versus treatment responsive EoE.

Methods

Patient selection

We prospectively enrolled subjects into a continuously accruing database at the University of California, San Diego (UCSD)/Rady Children's Hospital, San Diego(RCHSD). Informed consent/assent was obtained at the time of a standard of care clinic or endoscopy visit. All studies were approved by the UCSD/RCHSD Institutional Review Board (protocol 091485). Medical records were evaluated for clinical, endoscopic, laboratory, and histologic features and entered into a CTRI-housed Research Electronic Data Capture (REDCap) database. Data that had not been prospectively entered into the database was gleaned using chart review. The database was studied based on enrollment between 2011-2015 due to a transition in the UCSD/RCHSD electronic medical record to the "Epic" system in 2011. During this interval, there were 362 total subjects (Supplemental Figure 1). Subjects studied herein (n=146 of 362) met the following criteria: 1) EoE defined as ≥ 15 eosinophils per high powered field (hpf); 2) the presence of typical symptoms and endoscopic features of EoE; 3) treatment follow-up at UCSD/RCHSD for ≥ 2 years; and 4) ≥ 3 or more endoscopies in the follow-up time.

Clinical assessment

Clinical data including patient demographics, allergy testing, therapy, and symptoms were collected at baseline and at follow up visits. BMI was assessed at the first and last encounter. Allergy testing was performed using either skin prick testing (SPT) or allergen-specific serum IgE. Subjects with positive SPT or IgE testing to milk, egg, soy, wheat, peanuts, nuts, fish, or shellfish were noted to have food sensitization. Subjects with prior history of immediate hypersensitivity clinical response to a food with

concurrent positive IgE to the food were noted to be food allergic. Subjects with either positive SPT or allergen-specific serum IgE to any perennial or seasonal aeroallergen were noted to have aeroallergen sensitization. If testing was done at an outside center but reported to be positive by the family, these subjects were considered food and/or aeroallergen allergic at the time of entry into the study.

Therapy at each visit was coded as follows: 1) No therapy; 2) PPI; 3) Topical corticosteroid as oral viscous budesonide or swallowed fluticasone; 4) Elimination diet (usually 6 food elimination diet or elemental formula plus food(s)); 5) Elimination diet + PPI; 6) Topical corticosteroid + PPI; 7) Elimination diet + Topical corticosteroid + PPI.

Symptom and medication compliance assessment

At each visit, symptoms of heartburn/regurgitation, nausea/vomiting, dysphagia, abdominal pain, and nocturnal awakening were recorded using subject and/or parent completed symptom score.¹⁶ If symptom scores were not completed, symptom data was collected via chart review. Subjects were categorized as “symptomatic” or “asymptomatic”. Patients’ compliance to treatment (medications or diet) was self-reported and recorded as “yes” or “no”. There was no system for tracking medication refills.

Endoscopic assessment

Seventy-six percent of all endoscopies were performed by a single pediatric gastroenterologist (RD). Initial endoscopy was done by any pediatric gastroenterologist at UCSD/RCHSD. Follow up biopsies were done almost exclusively by RD. Endoscopies were performed for clinical indications, and there was no standard length of time between the procedures. Our general clinical practice is to repeat the endoscopy

with biopsy after 2 months on PPI or elimination diet, after 3 months on topical corticosteroids, and annually to monitor endoscopic and histologic disease activity. We collected data based on endoscopic instance in order to generate patterns of histologic inflammation. Each “instance” represents an endoscopy with biopsy. Pallor, linear furrowing, plaques, concentric rings/strictures/narrowing, and friability were graded as present/absent (0/1) at each esophageal level for a total endoscopy score (maximum=15).¹⁶ The presence or absence of ulcers/erosions was noted. To maintain consistency in scoring, non-UCSD/RCHSD endoscopies were not scored.

Histologic assessment

Esophageal biopsies obtained at UCSD/RCHSD were evaluated by local pathologists and epithelial eosinophils were quantified as part of routine clinical care. The majority of diagnostic endoscopies performed at outside institutions had biopsy re-evaluation at RCHSD; 3% of biopsies were not available for re-evaluation. We utilized the average eosinophils per high power field (hpf) from the peak eosinophil counts in the proximal, middle, and distal esophagus to gauge pan-esophageal disease burden. Disease was considered “controlled” when the average eosinophil count was <15 per high power field.

Statistical analysis

We compared categorical and continuous measures across groups with Fisher’s exact test and the Kruskal-Wallis test, respectively. When controlling for factors such as age and gender or modeling possible interactions, linear and logistic regressions were used for continuous and categorical outcomes, respectively. For measures with a longitudinal component (such as EGD scores or the probability of being symptomatic over time), we

190 used linear and logistic generalized estimating equations and generally assumed an
191 exchangeable working correlation. Correlations between continuous measures with
192 longitudinal components and their analytic 95% confidence intervals were computed
193 using the techniques of Bland and Altman. We considered p-values below .05 to
194 indicate statistical significance.

195

Results

Clinical characteristics

146 subjects met the entry criteria for analysis (Supplemental Figure 1). The majority were male (70.5%) and the average age at diagnosis was 7.23 years (Table 1). Length of follow-up ranged from 2-13 years, with an average of 5.13 years. The majority of patients had symptomatic allergic rhinitis (84%), consistent with a high rate of aeroallergen sensitization on skin prick or serum testing (69%). Seventy percent were allergic to pollen, while 46% were sensitized to dust mite and 43% to animal dander. Six subjects were on subcutaneous immunotherapy for environmental allergens. Fifty-five percent of patients were considered food allergic; 51% of subjects had positive IgE testing to foods. Other atopic diseases such as eczema and asthma were present in approximately half of the patients. Eight percent of patients had autoimmune or other inflammatory diseases including autoimmune hepatitis, celiac disease, type I diabetes, thyroid disease, and inflammatory bowel disease, in particular Crohn's disease (Table 1).

Trending eosinophilic inflammation over time reveals three distinct longitudinal eosinophil patterns

Each "instance" was defined as an endoscopic procedure with an accompanying esophageal biopsy. Plotting the average eosinophils per hpf longitudinally by instance identified 3 patient groups with distinct patterns of eosinophilic inflammation. The definitions for each group were not preconceived; rather, we plotted the average of eosinophils for all 146 patients who met entry criteria. Three distinct patterns of eosinophilia over time emerged upon initial graphic analysis. Children had either largely controlled disease with persistently low esophageal eosinophilia, waxing and waning

disease with recurrent peaks and valleys of esophageal eosinophilia, or persistently elevated esophageal eosinophilia over time (Figure 1a). We binned these 3 longitudinal EoE disease patterns into groups that we termed continuous responders (CR), intermittent responders (IR), and non-responders (NR). We then defined CR as patients as those who had $\geq 75\%$ of follow up biopsies ("instances") with < 15 average eosinophils per hpf. IR patients were defined as children with greater than 25% but less than 75% of follow-up biopsies showing < 15 average eosinophils per hpf. NR were defined as subjects who had $\leq 25\%$ of their follow up biopsies showing < 15 average eosinophils per hpf. 59 (40%), 65 (45%), and 22 (15%) of the 146 patients were CR, IR, and NR, respectively (Supplemental Figure 1a). Among CR, IR, and NR there were significant differences in the average eosinophils over the entire time of follow up (Figure 1b). The distal esophagus had the highest numbers of eosinophils as compared to middle and proximal esophagus in all of the responder groups. Middle, distal, and proximal esophageal eosinophils were significantly lower at all esophageal levels in the CR group and all groups had pan-esophageal eosinophilia, suggesting that no single area of the esophagus was the most difficult to treat (data not shown).

The number of subjects per endoscopic instance diminished to less than 5 subjects per group by instance 11 and there were no NR patients after instance 12 (Supplemental Figure 1b). Due to the low patient numbers in the later instances, endoscopic instances 1-10 were used in the analyses.

Responder Category is Not Directly Linked to Therapy Type

All of the patients enrolled in the study received standard-of-care EoE-directed medical management, including PPIs, swallowed topical steroids, food elimination, or a

combination of these treatments. A heat-map depicting the treatment course of each patient over time is shown in Figure 2. Patients shifted therapeutic regimens through their course and no single therapy predominated any one group. The majority of patients in all groups had initial endoscopy while on no therapy (101) or on PPI alone (38) (Figure 2). Self-reported compliance with therapy was high and only 5% of instances had documented self-reported non-adherence to the prescribed regimen. There were significantly more self-reported instances of non-compliance in the IR (17 non-compliant instances of total 316 instances) and NR (13 non-compliant instances of 108 total instances) groups as compared with the CR group (1 non-compliant instance of 215 total instances) ($p<.001$). Episodes of non-adherence occurred throughout follow-up (outlined boxes in heat map) but there were many more instances of compliance as compared with non-compliance (Figure 2).

There were some treatment differences between the groups, with more food elimination in the IR and CR groups, though numbers of these were overall low. Six food elimination diet was tried by 9 IR (13.8%), 1 NR (4.5%) and 6 CR (10.1%). There were 13 patients in the CR who tried only PPI, versus 4 in the IR and 1 in the NR group. There were 18 CR patients whose last endoscopy was off all EoE directed therapy (Figure 2), with 16 of 18 maintaining histologic control (11% of the entire cohort, 27% of the CR group, and 89% of those that were off therapy in the CR group). Of the CR patients with eosinophilic control at the last biopsy, 39% were initially PPI-responsive EoE. The IR group had 12 subjects off therapy with 3 maintaining <15 eosinophils per hpf on the last biopsy (8% of the entire cohort, 4.6% of the IR group, and 25% of IR that were off therapy). Three NR group subjects were off therapy at the last biopsy and none

had <15 eosinophils per hpf.

Clinical features by responder group over time

Demographic characteristics

There were some key differences in the clinical features between the groups. Males predominated the IR and NR groups but the CR group was evenly distributed between male and female sex ($p<.01$) (Table 1). When compared to the CR group, the odds of being male was 3.99 times (CI: 2.83 to 5.68) higher in the IR group and was 6.09 times (CI: 3.45 to 11.33) higher in the NR group. There were no significant differences in the age at diagnosis or the number of years of follow up among the 3 groups, but NR patients tended to be younger at diagnosis.

Using a multivariate regression analysis, the predictors of continuous response were female sex (odds ratio=2.95, 95% CI 1.26, 7.14, $p=.014$) and initial complete response to therapy (defined as <15 eosinophils per hpf) (OR=9.97, 95% CI 4.20, 26.81, $p<.001$). We analyzed if PPI response as the initial therapeutic response was more likely to predict being a CR. Univariate analysis demonstrated a significant effect of PPI response on the odds of being a CR patient (OR=11, 95% CI 4.7, 29, $p<.0001$). However, when used in a multivariable model with sex, general initial response to any therapy, and allergic rhinitis, PPI response did not significantly influence responder category. Together, this data demonstrates that sex and initial response to any therapy are the factors that influence the likelihood of being in the CR group.

Atopic Features

More subjects in the IR group had allergic rhinitis ($p=0.05$) (Table 1). When controlling for age as a covariate (adolescents defined as >13 years old) in a logistic

regression, the difference in allergic rhinitis became significantly higher in the IR group ($p<.05$) which likely reflects the onset of allergic rhinitis symptoms in older children.¹⁷ Food and environmental sensitization by skin prick and serum IgE were not significantly different among groups. In addition, the rates of asthma, eczema, oral allergy syndrome, and food allergy were not different between groups.

Body Mass Index (BMI)

CR had significantly lower BMI percentile for age at diagnosis, especially among males ($p<.05$) (Supplemental Figure 2a). At the end of follow up, there were no differences in BMI percentiles among the groups when males and females were grouped together. In addition, the change in BMI trended upward or remained static for all the groups and sexes except female non-responders who significantly decreased their BMI from the first to the last instance (Supplemental Figure 2b) ($p<.05$).

Symptoms over time

We also modeled the trajectory of symptoms over time as present or absent.¹⁶ The probability for being symptomatic decreased over time ($p<.01$) but there were no significant differences between groups in the trajectory of symptoms decline (Supplemental Figure 3a). For all patients, the probability of being symptomatic was lower when the average eosinophil count was less than 15 (odds ratio=0.32, 95% CI 0.24, 0.44, $p<.001$) but the rate of decrease in symptoms between controlled and uncontrolled eosinophilia was not different (Supplemental Figure 3b). When removing the group of subjects with concurrent intestinal autoimmune disorders (Crohn's and Celiac diseases), the relationship between responder group and the probability of being symptomatic became significant ($p<.01$). With removal of the autoimmune GI group, the

NR group had a significantly higher odds ratio for being symptomatic when compared to CR (OR 2.09, 95% CI 1.276 – 3.824). No other outcomes were altered.

Endoscopic Features

The number of endoscopies ranged from 3 to 20 and there were significantly fewer endoscopies in the CR group as compared with the IR and NR groups ($p<.05$). This was likely accounted for by the shorter follow up time for CR patients. When normalized for annual endoscopies, there were no differences between the groups for the number of endoscopies per year (Table 2). IR and NR groups had significantly higher EGD scores overall and at baseline than CR ($p<.001$) (Figure 3a-c). When tracking the trajectory of the change in EGD scores over time, there were no differences in between the groups (Figure 3c). Interestingly, while the IR and CR groups had decreases in their EGD scores over time, the NR had increases in their EGD scores, suggesting a progressive disease course despite therapy in NR patients(Figure 3c).

There were no significant differences in the more severe endoscopic features of rings or strictures between the groups over time (Supplemental Table I). One CR, 5 IR and 2 NR had strictures. Two subjects had strictures at diagnosis which resolved at instances 2-5 (IR) and instances 10-12 (NR). The one CR patient with a stricture had stricture onset while on PPI; this stricture resolved with dilation and therapy on all the subsequent instances (3-8). Overall, 5% ($n=8$) of patients had endoscopic rings or strictures, 6 subjects had the onset of strictures during therapy and 5 of these were IR or NR subjects. Two patients had strictures that were present over multiple endoscopies and both were male. There were no differences in eosinophils per hpf at the time with (56 per hpf) versus without (36 per hpf) stricture. No strictures were from

patients with tracheoesophageal fistula. Erosions were identified in all groups and were evenly distributed (Supplemental Table I).

Given that the trajectory of the EGD scores over time appeared to align with eosinophilic inflammation (Figure 1a, 3b), we sought to understand the relationship between endoscopic and eosinophilic severity. Tracking the association of these two features over the entire follow up demonstrated that EGD scores were positively correlated with average eosinophils per hpf (Figure 3d, $r=0.73$, $p<0.001$).

Peripheral eosinophils over time

An analysis of peripheral eosinophil counts demonstrated that NR had a higher overall peripheral eosinophilia (absolute eosinophil count= 579) as compared with CR or IR groups (absolute eosinophil counts 406 and 503, respectively) ($p<.01$ for CR versus NR). IR patients had a static trajectory and CR patients had a decreasing trajectory of peripheral eosinophilia over time. In contrast the NR group had an increasing peripheral eosinophilia over time (Figure 3e). The NR group had the strongest correlation between peripheral and esophageal eosinophilia ($r =0.46$, $p<.001$) suggesting that peripheral eosinophils may be a biomarker for esophageal eosinophilia in therapy non-responsive subjects (Supplemental Table II).

Discussion

In this longitudinal single center pediatric EoE cohort study, we report a number of compelling and potentially clinically impactful findings. First, we identified three distinct histologic disease response patterns to standard of care EoE therapy over an average of 5.13 years of follow up. Second, we documented significant differences in the sex distribution between the three groups with females having 3 times the odds of males for long-term esophageal inflammatory control. This aligns with adult data showing that female sex associates with the likelihood of “deep remission”.^{5, 18} Third, we found durability of therapeutic response in 40% of patients and intermittently controlled disease in an additional 45%, suggesting that, in >80% of children, there can be good histologic EoE control. Importantly, the initial response to therapy was an indicator of subsequent longitudinal disease course with CR having 10 times higher odds of continued inflammatory control as compared with IR and NR groups. Among CR patients who had eosinophilic control at their last biopsy, approximately half were PPI responsive EoE, consistent with the notion that this represents a milder EoE phenotype. Fourth, histologic control associated with endoscopic control and, in the NR group, the severity of esophageal and peripheral eosinophilia correlated significantly, suggesting that endoscopic features and/or peripheral eosinophilia may be adequate surrogates for histology in some patients. Of note, we opted to utilize the average eosinophils per hpf through the esophagus in order to get the best reflection of pan-esophageal disease burden which is important when comparing other pan-esophageal features such as endoscopy scores. Lastly, our patients maintained a healthy BMI which aligns with the findings of a short 1 year study.¹⁹

There is currently no personalization to the time between endoscopies, and this

is a challenge to researchers in trending patterns of eosinophilic inflammation. Here we have chosen to track the eosinophils based on endoscopic instance, which is currently the only manner in which to monitor EoE. There are no established clinically guiding cues for which patients may tolerate interventions such as medication dose reductions, a trial off medications, and/or dietary additions while eliminating foods.^{5, 7} There is always the concern that if therapy is stopped and inflammatory control is not regained on EoE recurrence then the patient will be at risk for complications such as progression to stricture.^{18, 20-21} We had very few subjects who reportedly stopped therapy. However, our data suggests that the clinical parameters of initial response to any therapy, including PPI, and/or female sex can help predict those patients who may tolerate less aggressive therapeutic regimens, who are at lower risk for stricture formation, and who may tolerate increased time intervals between endoscopic procedures. Since the duration of remission in EoE is unclear, it would be essential to continue endoscopic follow up. This is consistent with other studies that have shown rate of relapse correlating with the duration of follow-up.⁸ Our CR patient group likely represents an easier to treat EoE phenotype and their distinguishing clinical characteristics may help to guide future prospective and interventional studies. Given the nature of our study design, it is also possible that CR patients are simply more a therapy-adherent population.

We readily acknowledge the weakness that, like any real-world longitudinal cohort, our population of children may have not adhered continuously to the prescribed regimen. However, it seems unlikely that medication adherence is the full explanation for the distinct longitudinal inflammatory patterns since all responder groups' families

came over multiple years for endoscopies, which is costly in dollars, time, and perceived procedural risks. In addition, the number of instances during which there was documented non-adherence to therapy was low in all the groups. We did find that the CR group had significantly lower rates of noncompliance with therapy. This speaks to a number of possibilities. One could conclude that patients are CR if they regularly take their medications. Alternatively, one could conclude that the esophagi of CR patients is intrinsically milder in a molecular or physical manner that makes them easier to treat and that the ease of treatment is positive clinical reinforcement for continued adherence to the prescribed regimen. Given the adult finding that the fibrostenotic esophagus is hard to treat, it is likely that the NR, and perhaps the IR, groups have currently unappreciated differences in their esophagi, such as persistent mucosal resistance abnormalities or subclinical esophageal rigidity or narrowing. Our findings also speak to the need for education regarding the chronic use of medications and elimination diets, especially in NR patients, and the pressing requirement for novel and FDA approved therapies.²² We could expect that adherence may vary over time in this chronic disease. Monitoring for adherence will be important in future natural history studies and our data support the need for vigilance by providers in assessing medication and dietary compliance as well as the methods of utilization (e.g. mixing ingredients). In contrast, the strength of our study is the potential general applicability to the EoE population since an observational cohort likely reflects more usual therapy adherence patterns. Future research will determine how representative our population is among the broader population of patients with EoE since our patients were cared for at a tertiary academic center which could introduce a selection bias for a more severe or refractory population.

Despite its limitations, the delineation of distinct responder groups in our study points out the potential for distinct management strategies by initial response and sex; such as less frequent endoscopies in subjects who are female and initial responders. Such strategic alterations in management would be beneficial to patients.

Only a minority of subjects had sustained histologic response off therapy but, like adults, there was durability of response to continued therapy in a large proportion of patients.^{5, 10, 23} Only IR and NR patients had rings or strictures at their initial visit and more IR and NR had ensuing strictures as compared with CR. As in adults, this suggests that an endoscopically fibrostenotic esophagus is harder to treat even in children.²⁴ We did see two quite refractory strictures in our IR and NR groups, lending support to the hypothesis that length of time with elevated eosinophils contributes to fibrosis.¹⁵ Our IR and NR were overwhelmingly male, which also correlates with increased risk of stricture in this population.¹⁸ NR and IR populations likely represent those patients who will need chronic therapy. IR children, especially those older than 13 years, had higher rates of allergic rhinitis. Since environmental allergies can exacerbate EoE-associated eosinophilia²⁵, changing loads of triggers such as pollens could theoretically account for the volatility of their eosinophilic inflammation over time, as could the introduction of seasonally available foods. We did not study the association of pollen triggers and esophageal inflammation since many of our subjects were sensitized to perennial aeroallergens (dust mite, animals, and grass that pollinates 9 months of the year in Southern California). However, it seems that IR patients may benefit from therapies that optimize control of their allergic rhinitis including control of environmental antigens or from allergen immunotherapy.

There are no surrogate markers for EoE. Symptoms are not known to correlate with inflammation longitudinally. For our patients, there was loss of symptoms over time, which may reflect compensatory behaviors. In addition, the clinical disconnect between symptoms and inflammation is underscored by the fact that symptoms were present even when eosinophils were controlled. The longitudinal assessment of symptoms using validated scoring tools such as the PEESV2.0 may help to better define symptoms that correlate with histology.²⁶ Peripheral eosinophils correlated with esophageal eosinophils in NR patients and blood eosinophilia may perform as a surrogate marker in subgroups of patients.

In conclusion, our data suggest that female children who respond initially to any EoE-directed therapy continue to have an adequate therapeutic response. Further, children appear to be at risk for fibrostenotic complications when therapeutic response is not achieved and/or maintained and children with strictures may be more difficult to treat. Allergic rhinitis may modulate EoE course and targeting aeroallergen immune response or exposure could be a useful adjuvant therapy. It will be interesting to understand if our findings are broadly applicable to the EoE population since defining optimal chronic EoE management is a pressing need, especially in children.

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Table I. Features of Children with EoE

	Overall (n = 146)	Continuous Responder (n = 59)	Intermittent Responder (n = 65)	Non-Responder (n = 22)	p-value
Gender					
Female	43 (29.5%)	27 (45.8%)	13 (20.0%)	3 (13.6%)	0.002**
Male	103 (70.5%)	32 (54.2%)	52 (80.0%)	19 (86.4%)	
Age at Diagnosis					
Mean (SD)	7.23 (4.88)	7.25 (5.00)	7.54 (4.69)	6.23 (5.21)	0.361
Median (Range)	7 (0, 18)	7 (1, 18)	8 (0, 17)	4 (1, 16)	
Years Followed					
Mean (SD)	5.13 (1.86)	4.69 (1.41)	5.43 (2.14)	5.41 (1.92)	0.158
Median (Range)	5 (2, 13)	4 (2, 9)	5 (2, 13)	5 (3, 9)	
Eczema	71 (48.6%)	25 (42.4%)	33 (50.8%)	13 (59.1%)	0.389
OAS	6 (4.1%)	3 (5.1%)	2 (3.1%)	1 (4.5%)	0.864
Asthma	75 (51.4%)	29 (49.2%)	34 (52.3%)	12 (54.5%)	0.924
Allergic Rhinitis (AR)	123 (84.2%)	46 (78.0%)	60 (92.3%)	17 (77.3%)	0.050*
Food Allergy (FA)	80 (54.8%)	29 (49.2%)	36 (55.4%)	15 (68.2%)	0.322
Positive Aero Allergen Testing	100 (68.5%)	39 (66.1%)	48 (73.8%)	13 (59.1%)	0.379
Positive Food Allergen Testing	74 (50.7%)	26 (44.1%)	36 (55.4%)	12 (54.5%)	0.456
Auto-immune Disease					
Autoimmune Hepatitis, IBD	1 (0.7%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0.731
Celiac	2 (1.4%)	2 (3.4%)	0 (0.0%)	0 (0.0%)	
DM1	2 (1.4%)	0 (0.0%)	2 (3.1%)	0 (0.0%)	
Hypothyroidism	1 (0.7%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	
IBD	5 (3.4%)	2 (3.4%)	2 (3.1%)	1 (4.5%)	
Any Auto-immune Disease (AI)	12 (8.2%)	6 (10.2%)	5 (7.7%)	1 (4.5%)	0.778
Change in BMI Percentile^a					
Mean (SD)	3.48 (24.86)	6.89 (26.59)	1.33 (16.88)	0.66 (37.52)	0.659
Median (Range)	0.49 (-83.18, 76.27)	1.38 (-47.88, 76.27)	0.31 (-32.8, 51.7)	-0.36 (-83.18, 75.2)	

^a5 missing values; DM1: diabetes mellitus, type 1; IBD: inflammatory bowel disease

Figure Legends

Figure 1. Distinct esophageal eosinophilic inflammatory patterns over time. Mean eosinophils per hpf in the esophagus over time by responder group (A). Average eosinophil counts over the entire follow up time by responder group (B).

Figure 2. Therapies utilized in each group. Heat map of therapy by instance (x-axis) by responder group. Each row represents a unique patient. Asterisks reflect instances with average eosinophils <15 per hpf. Outlined boxes indicate episodes of self-reported non-adherence to the prescribed regimen.

Figure 3. Longitudinal endoscopy scores and eosinophilia. Overall EGD scores by group (***: $p < .001$) between groups (A). Mean EGD scores (B) and regression lines for score trajectory by responder group (C) over instances (**: $p < .01$). The relationship between EGD scores and mean esophageal eosinophil count (D). The peripheral eosinophil trajectory over time by group (*: $p < 0.05$ between NR and CR trajectories) (E).

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A

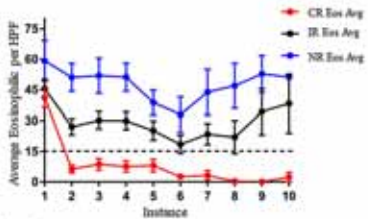
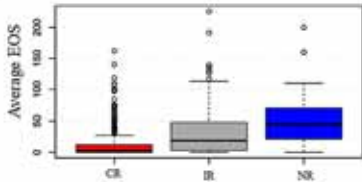


Figure 1.

B



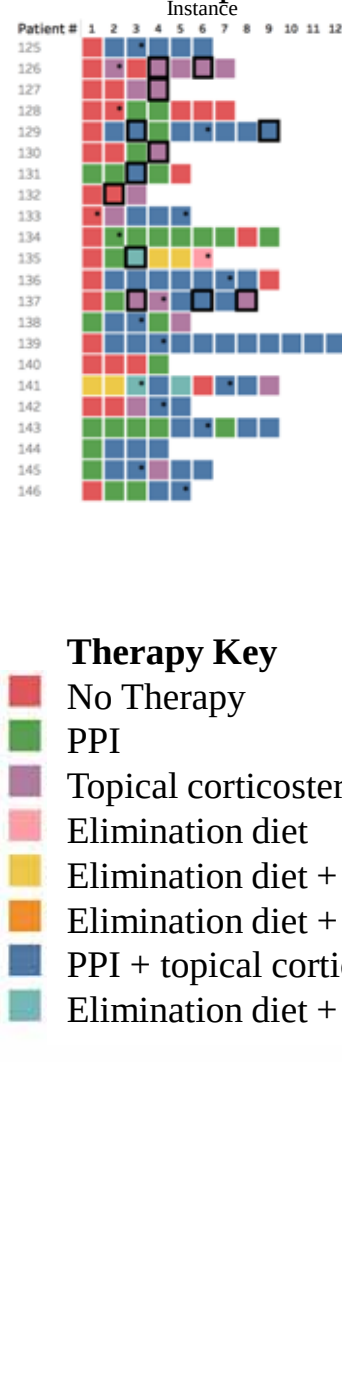
Continuous Responder



Intermittent Responder



Non-Responder



Therapy Key

- No Therapy
- PPI
- Topical corticosteroid
- Elimination diet
- Elimination diet + PPI
- Elimination diet + topical corticosteroid
- PPI + topical corticosteroid
- Elimination diet + PPI + topical corticosteroid

Figure 2

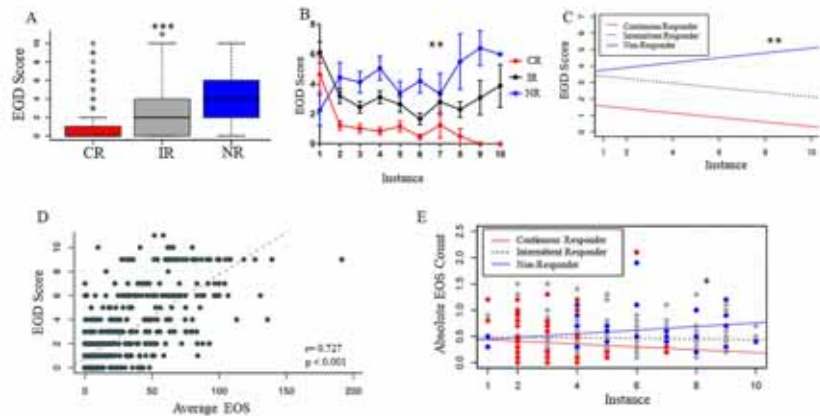


Figure 3

Long-term Course of Children with Eosinophilic Esophagitis Reveals Distinct Histologic Patterns and Clinical Characteristics

Cathleen Collins*, M.D., Ph.D.^{1,3}, Jacob Palmquist*, M.D.^{1,3},
James A. Proudfoot, M.S.,^{1,3,5} Alex Qian, B.S.^{1,3}, Hannah Wangberg, M.D.^{1,3,4},
Emad Khosh-Hemmat, B.S.^{1,3}, Ranjan Dohil, M.D.^{2,3}, Seema S. Aceves, M.D., Ph.D.^{1,3,4}

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Supplemental Figure 1. Subjects per responder group. Numbers of subjects in each responder group (A). Number of subjects per responder group over all 20 instances (B).

Supplemental Figure 2. BMI over time. BMI percentiles at diagnosis and at final instance broken down by biologic sex per group (*: $p < 0.05$ for CR versus other groups for BMI at diagnosis) (A). Change in BMI over time by biological sex and responder group (*: $p < .05$ for difference between female NR versus CR and IR) (B).

Supplemental Figure 3. Symptoms over time. Probability of being symptomatic by instance in each responder group (A) and in the cohort during times of uncontrolled (eosinophils ≥ 15) or controlled (< 15 per hpf) eosinophilia (B).

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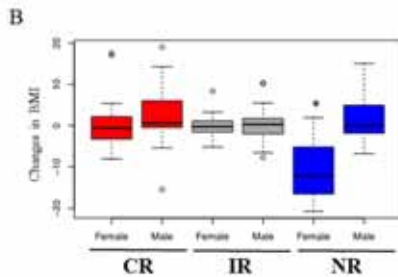
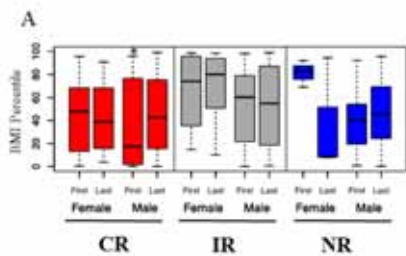
Funding Sources: NIH/NIAID AI092135 (S.S.A.), NIH/NIAID AI135034 (S.S.A.), NIH UL1TR001442 (J.A.P)

Supplementary Table I. Endoscopic Features

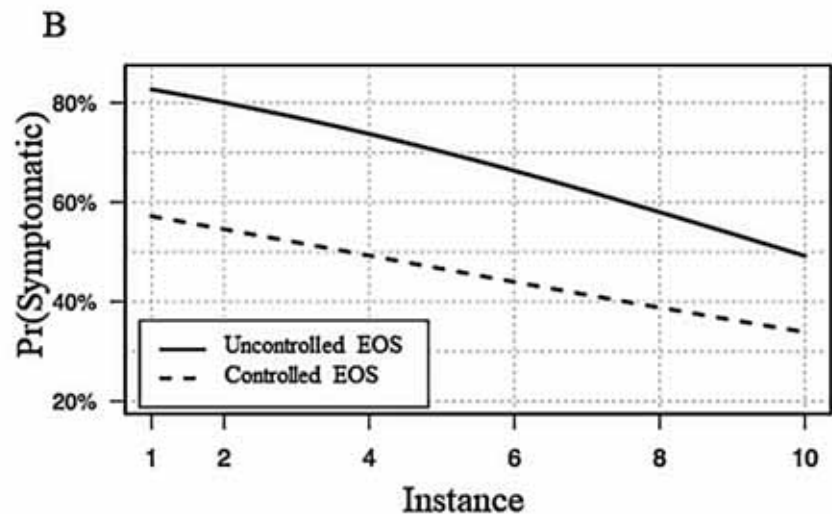
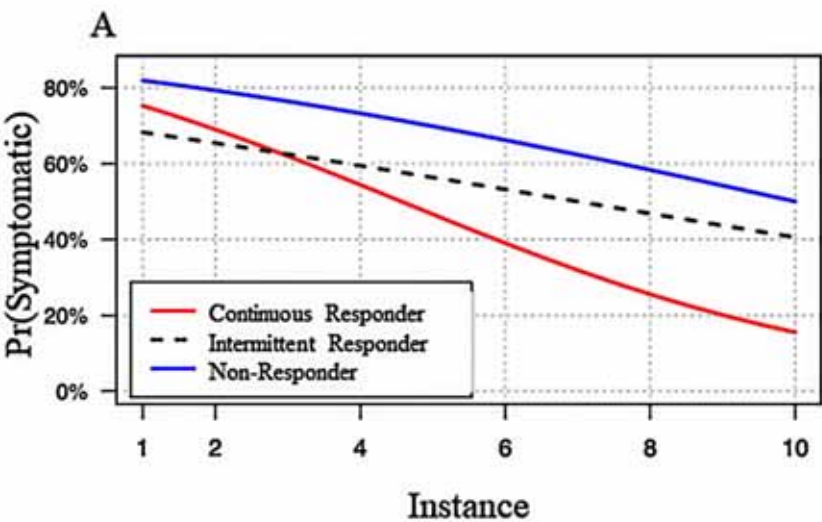
	Overall (n = 146)	Continuous Responder (n = 59)	Intermittent Responder (n = 65)	Non- Responder (n = 22)	p- value
Total Endoscopies	5.99 (3.15) 5 (3, 20)	5.20 (2.22) 5 (3, 15)	6.57 (3.91) 6 (3, 20)	6.41 (2.32) 6 (3, 12)	0.023*
Total Endoscopies / Years Followed	1.23 (0.60) 1.14 (0.44, 4.00)	1.16 (0.51) 1.00 (0.60, 3.75)	1.27 (0.65) 1.17 (0.46, 4.00)	1.33 (0.68) 1.23 (0.44, 3.00)	0.502
History of Erosions					
No	71 (48.6%)	28 (47.5%)	33 (50.8%)	10 (45.5%)	0.901
Yes	75 (51.4%)	31 (52.5%)	32 (49.2%)	12 (54.5%)	
History of Rings / Strictures					
No	138 (94.5%)	58 (98.3%)	60 (92.3%)	20 (90.9%)	0.210
Yes	8 (5.5%)	1 (1.7%)	5 (7.7%)	2 (9.1%)	

Supplementary Table II. Correlation between peripheral and esophageal eosinophils in the entire cohort and separated by group.

	Overall	Continuous Responder	Intermittent Responder	Non-Responder
Correlation	0.290	0.311	0.225	0.470
95% CI	(0.160, 0.411)	(0.062, 0.523)	(0.036, 0.399)	(0.177, 0.687)
p-value	<0.001***	0.002**	0.014*	<0.001***

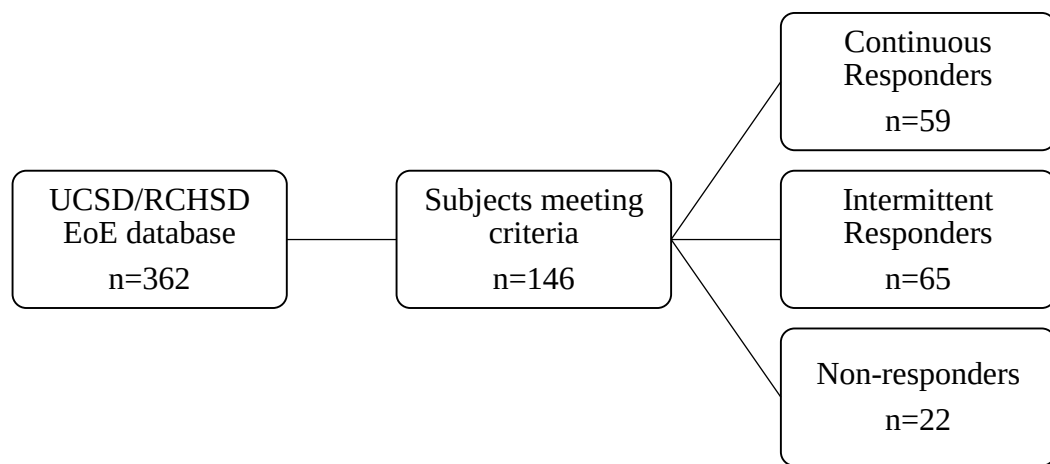


Supplemental Figure 2

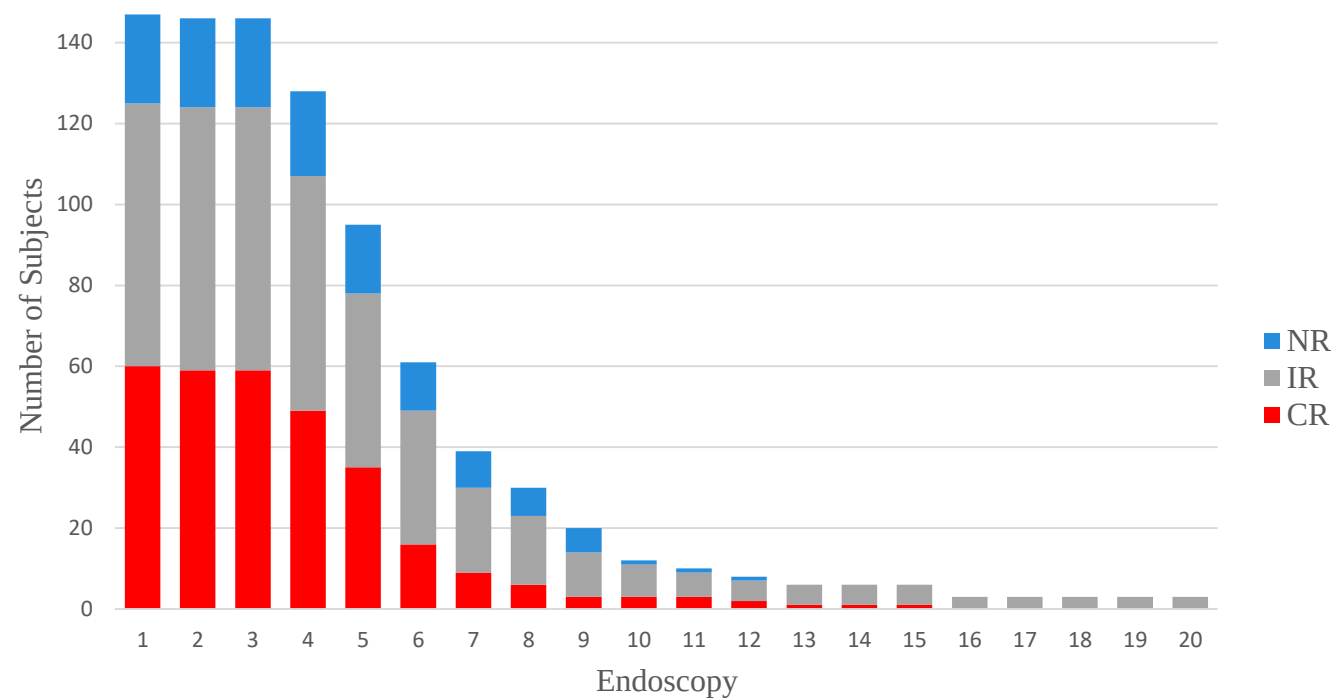


Supplemental Figure 3

A



B



Supplemental Figure 1