A Retrospective Review of Medical Gastrointestinal Endoscopy in Children Attending Red Cross War Memorial Children's Hospital, Cape Town

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DECLARATION

I, EKE CHRISTOPHER BISMARCK, hereby declare that the work on which this dissertation/thesis is based is my original work(except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or other university.

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ABSTRACT

Background: Gastrointestinal endoscopy has evolved to become an important diagnostic, therapeutic as well as surveillance and follow-up modes of management in children with diverse gastrointestinal diseases.

There is a paucity of data on gastrointestinal endoscopy in children in the sub- Saharan African region. The objectives of the study were to describe the socio-demographic characteristics; presenting symptoms; indications; endoscopic yield; impact of endoscopy on management; as well as its safety profile and complications. In addition algorithms for the indications of medical gastrointestinal endoscopy in children were designed using the results derived from the presenting symptoms and indications for gastrointestinal endoscopy among the patients.

Methods:

This was a cross sectional descriptive study. Subjects were children < 18 years attending Red Cross War Memorial Children's Hospital (RCWMCH) who underwent medical gastrointestinal endoscopic procedures from 2007 to 2016.

Study ethical approval was obtained from University of Cape Town while written permission from the RCWMCH Research and Management Committee prior to the commencement of the study.

Data sheet was used in retrieving relevant patients variables from the hospital's medical records and the Division of Paediatric Gastroenterology endoscopy and laboratory (histopathology) databases.

Data was analysed using Stata 13.1. A p- value of less than 0.05 was considered statistically significant.

Results:

A total of 402 children were studied with 773 endoscopies performed comprising 670 oesophagogastroduodenoscopies (OGD) and 103 colonoscopies.

For OGD: 179 (26.7%), 287(42.8%) and 204 (30.4%) procedures were for diagnostic, therapeutic and follow – up indications. A total of 78 (10.1%) combined OGD/colonoscopy were carried out.

Out of 103 total colonoscopies performed, 67 (65.0%), 30(29.1%), and 6 (5.8%), were for diagnostic, follow – up and therapeutic indications respectively.

Feeding difficulty 112 (25.4%) and rectal bleeding 11 (2.7%) were the main presenting symptoms for OGD and colonoscopy respectively.
Main diagnostic indications for OGD, combined OGD/colonoscopy and colonoscopy alone respectively were chronic abdominal pain 51 (12.6%) and probable inflammatory bowel disease (IBD) 30 (7.5%) and IBD 30 (7.5%). Change 143 (35.6%)/ insertion 87(21.6%) of percutaneous gastrostomy were the most common therapeutic indications for OGD and polypectomy 8 (2.7%) for colonoscopy.

Abnormal (positive) macroscopic findings on endoscopy were reported on 79/179(44.1%), 35/68(51.55%), and 46/67(53.7%) of OGD, combined OGD with lower scope, and colonoscopy alone respectively.
Also, positive histological findings on OGD, combined OGD with colonoscopy, and colonoscopy alone were reported in 62/179(34.6%), 34/68(50.0%), and 32/67(47.8%) respectively.
The overall normal endoscopic findings (both abnormal macroscopic findings on endoscopy and histological findings) were 63/179(35.3%) and 25/67(37.3%) for OGD and colonoscopy while overall diagnostic (endoscopic) yield was 116/179(64.8%) for OGD and 42/67(62.7%) for colonoscopy respectively.
For OGD the main endoscopic yield reported were gastritis in 50(27.9%) and oesophageal varices 31(17.3%) while inflammatory bowel disease (Crohn's disease 9(13.4%), ulcerative colitis 7(10.4%), juvenile polyps 9(13.4%) and intestinal tuberculosis 7(10.4%) were observed in colonoscopy respectively.

A significant impact of endoscopy on the management of subjects were recorded in 298(74.1%) ($p < 0.001$) including diagnostic (change of medication, addition of new medication) and therapeutic (insertion/change of PEG; sclerotherapy 29 (9.8%) , band ligation of oesophageal varices 28 (9.4%), and polypectomy 8(2.7%)).
The overall complication rate was 4.0% (16 patients).

Conclusion:
Feeding difficulty and rectal bleeding were the most common presenting symptoms for OGD and colonoscopy; with chronic abdominal pain and IBD being the most common indication for performing OGD and colonoscopy respectively. Therapeutic modalities of endoscopy performed were PEG insertion/change, polypectomy, sclerotherapy/band ligation for varices.

Endoscopic yield was 116/179(64.8%) for OGD and 42/67(62.7%) for colonoscopy respectively a significant impact of endoscopy on the management of subjects were recorded in 298(74.1%) ($p < 0.001$).
No mortalities were recorded following the procedures, however 16(4%) had some complications.

Use of societal guidelines in selecting children with appropriate indications for gastrointestinal endoscopy will result in higher diagnostic yield and application of therapeutic modalities in children with gastrointestinal disorders resulting in significant impact on patient's management and minimize complications.

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To the staff of the medical records of Red Cross War Memorial Children's Hospital (RCWMCH) who assisted me during the pulling of the folders of the study subjects I say thank you.

To the many patients and their mothers/caregivers I have had the opportunity to be associated with during my training at The Division of Gastroenterology, Red Cross War Memorial Children's Cape Town I thank you all.

I am particularly grateful to my family for their support, prayers and encouragements which helped to motivate me during the period of study.

To Almighty God who strengthens me I give all the glory and adoration.

Eke Chris

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LIST OF ABBREVIATIONS

ASA	American Association of Anaesthesiologists
CMV	Cytomegalovirus
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
EoE	Eosinophilic Oesophagitis
FTT	Failure to Thrive
FWACPaed	Fellow West African college of Physicians (Paediatrics)
GORD	Gastroesophageal reflux disease
H0/H1/H2/ or H3	Tariff category
H. pylori	Helicobacter pylori
HREC	Health Research Ethics Committee
IBD	Inflammatory Bowel Disease
ICD10	10th Revision of the International Statistical Classification of Diseases and Related Problems
JPGN	The Journal of Pediatric Gastroenterology and Nutrition
NASPGHAN	North American Society for Pediatric Gastroenterology Hepatology and Nutrition
OGD	Oesophagogastroduodenoscopy
PCR	Polymerase Chain Reaction
PEG	Percutaneous endoscopic gastrostomy
PUD	Peptic Ulcer Disease
RCWMCH	Red Cross War Memorial Children's Hospital
TB	Tuberculosis
UCT	University of Cape Town
WCE	Wireless Capsule Endoscopy

CHAPTER ONE: INTRODUCTION

1.1 Context

Gastrointestinal endoscopy in children has evolved to become an important diagnostic, therapeutic and surveillance modes of management in children with gastrointestinal disorders[1] owing to the technological advancements in endoscopy design and its devices.[2,3] Improvements in sedation, anaesthesia[4] and skills in monitoring of vital signs of patients,[5] during endoscopic procedures have added to the increased and safe use of gastrointestinal endoscopy in children and neonates[6] enabling the increase in the diagnosis of common as well as diagnostic dilemmas in paediatric gastrointestinal diseases including coeliac disease of which endoscopic biopsy is the gold standard diagnostic technique,[7]severe gastro-oesophageal reflux disease,[8] eosinophilic oesophagitis, and inflammatory bowel disease among others.[6]

Diagnostic and therapeutic modalities of gastrointestinal endoscopy are diverse and include oesophagogastroduodenoscopy (OGD), colonoscopy, polypectomy, haemostatic therapy, balloon dilation, and placement of percutaneous endoscopic gastrostomy (PEG) tube. These are fundamental to the assessment, treatment, and care of infants and children with various gastrointestinal disorders.[9]
It is essential that safety is maintained through acquisition of adequate medical knowledge and technological know-how specific to performing gastrointestinal endoscopic procedures in children,[10] in order to ensure effectiveness.

Medical gastrointestinal endoscopy in paediatric population ranging from neonates to adolescents is usually undertaken in most reference centres by certified paediatric gastroenterologists trained in accredited fellowship programmes,[2,9,10] who ensure that standard protocols are maintained including pre-procedure preparation of patients, peri-procedure maintenance as well as continued post-operative care.

Preparation for endoscopy in paediatric patients requires the physician paying attention to the child's physiology as well as the emotional and psychosocial wellbeing of both patient and his/her primary caregivers.[9] Early emotional, psychosocial support of the child and the parents/caregivers are beneficial in endoscopic procedures particularly in

centres where conscious sedation is used.[11] The parents/legal guardian of the child should be adequately counselled about the procedure and the child if s/he is old enough otherwise relevant role play models could be applied in counselling the younger child. However, in most tertiary centres with adequate anaesthetic support, general anaesthesia is preferred in children as it is associated with improved outcomes. Also in children less than three years, the airways have to be protected from the compression exerted by gastroscope as it is being passed, hence the preference for general anaesthesia.

Informed consent should be obtained from an appropriately designated parent or legal guardian as required by the State while assent should be obtained when appropriate from an older child.[9] When obtaining consent, the nature of the procedure including risks of anaesthesia and its possible complications should be explained.

These complications could be related to sedation/anaesthesia, procedure or patient's underlying condition and include hypoxia, bleeding, respiratory distress, nausea/vomiting, gut perforation, pneumoperitoneum among others. However the risks are very rare and by and large the therapeutic and diagnostic benefits of endoscopy by far outweigh these risks.[11,12,13,14] In a cross- sectional database review of the complications arising from OGD from 13 facilities between 1999-2003 that reviewed 10,236 procedures performed in 9234 paediatric patients, reported an immediate complication rate of 2.3% associated with OGD. The most common complications noted in that study were hypoxia (1.5%) and bleeding (0.3%). A higher complication rate was seen in the youngest children who desaturates easily, those with highest American Society of Anaesthesiologists class (ASA), or received intravenous sedation rather than general anaesthesia.[12]

Absolute contraindication should be identified prior to the procedure and include unstable airway, cardiovascular collapse, intestinal perforation and peritonitis, while relative contra-indication are bowel obstruction, severe thrombocytopaenia, coagulopathy, recent gastrointestinal surgery, respiratory infection and recent food intake prior to the commencement of the procedure as patient must be fasted as per protocol[3,15,16]

Further as part of the pre- colonoscopy preparations adequate bowel cleansing of the patient with standard bowel preparation regimens prior to the procedure is essential for

clear endoscopic field.[17] Various cleansing regimens including polyethylene glycol with electrolytes, polyethylene with normal saline enema, bisacodyl suppositories are in use either singly or in combination.[18] However, no standardized bowel preparation regimen or paediatric colon cleanliness index exists for children; recommendations have been made concerning pre-procedural preparation complemented by the individual experience of the specific endoscopic centres.[3] This bowel preparation should be emphasized so as to allow for a clear visible gut during the colonoscopy.

Some gastrointestinal endoscopic procedures require pre-procedural parenteral antibiotic prophylaxis such as during PEG tube insertion because of its high risk of infection. Antibiotic recommendation therefore has to be determined by a combination of procedure-related risk of bacteraemia and patients' risk,[12] and as well as local experience.

Patient's monitoring during endoscopic procedures is crucial for a successful procedural outcome. The American Academy of Paediatrics has issued recommendations regarding sedation and monitoring for diagnostic and therapeutic procedures in children.[19] These guidelines recommend continuous pulse oximetry, and heart rate monitoring at all levels of sedation by a dedicated trained attendant who is specifically assigned to monitor the child's vital signs including oxygen saturation, heart rate, respiratory rate, blood pressure and in some settings electrocardiography. Monitoring of vital signs during an endoscopic procedure is important particularly in younger children as they can desaturate easily without showing obvious signs and symptoms.[3]

Gastrointestinal endoscopy has stood out as an accurate and informative method of assessing upper and lower gastrointestinal disorders and the procedures should therefore be performed only in clinical conditions in which it has shown superiority over other diagnostic methods,[9] to improve its diagnostic yield and therapeutic impact on the management of patients.

Various leading societal expert groups including North American Society for Paediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) and European Society for Paediatric gastroenterology Hepatology and Nutrition (ESPGHAN) have assessed the different guidelines for the use of gastrointestinal endoscopy in children.[20] The objective

is to have a clear underlying evidence that findings from the endoscopic procedure will impact positively on patient's diagnosis and/or treatment.

Endoscopy is not usually indicated in older children for the evaluation of functional gastrointestinal disorders, including self- limited abdominal pain, constipation and incontinence.[21]Exceptional indications may include children with 'red flag' symptoms and signs such as abdominal pain waking the child up from sleep, other associated systemic symptoms like fever, joint pain or unusual rash, significant vomiting especially with bile or blood, recurrent mouth ulcers, associated malnutrition or poor growth; dysphagia; and mucous or blood in the faeces.[6]

Gastrointestinal symptoms including haematemesis, chronic abdominal pain, persistent vomiting, anaemia, dysphagia, and foreign body ingestion are indications for endoscopy. OGD is particularly useful in evaluating common paediatric foregut disorders including allergic, infectious, peptic oesophagitis and gastritis, coeliac disease, as well as diagnosis and treatment of strictures and variceal bleeding in children with portal hypertension arising from different aetiologies.[6,22]

Colonoscopy may be performed in infants and children with rectal bleeding. A diagnosis of inflammatory bowel disease can be established as well as defining the extent and the severity of the disease, which may identify complications and influence initial management. It can also be important in follow up assessment of disease progress. Further uses of colonoscopy may also include diagnosing causes of allergic colitis, colitis caused by other conditions like granulomatous diseases including mycobacterium organisms as well as lower gastrointestinal haemorrhage, chronic diarrhoea, cancer surveillance/follow up particularly in children with multiple polyposis syndrome.
Therapeutic colonoscopy is used in the management of polyps, foreign body removal, stricture dilatation, percutaneous caecostomy as well as reduction of intussusception.[23,24]

With further technological advancements newer modalities of endoscopy have been developed including small bowel enteroscopy and wireless capsule endoscopy. Wireless capsules passed via the oral route allow mucosal visualization of the small bowel (from the duodenum to the caecum) thus aiding the diagnosis of some gastrointestinal pathologies previously posing with diagnostic dilemmas including occult gastrointestinal

bleeding, suspected Crohn's disease, Coeliac disease, and small bowel polyps in individuals with hereditary polyposis syndromes.[3,25]

The sensitivity/diagnostic yield of all endoscopic examinations in paediatric patients varies with the age of the child and indication for the procedure. In upper gastrointestinal endoscopy, Chang and colleague, [26] reported an 85% ability of the OGD to pick up source of upper gastrointestinal bleeding in a cohort of 23 patients. In another study of 16 patients undergoing upper gastrointestinal endoscopy six out of the 16 patients (37.5%), had endoscopically detected abnormalities despite normal radiographic reports.[27]

The results of biopsy in endoscopic procedures have markedly improved the diagnosis of some gastrointestinal diseases including Helicobacter pylori infection related gastritis and small intestinal ulcers, Coeliac disease, inflammatory bowel disease (IBD) and associated secondary infections during acute flare up of ulcerative colitis including Cytomegalovirus colitis/infection.[28]
Tissues biopsies taken during colonoscopy from abnormal and even macroscopically normal parts of the gut have helped to diagnose some common differentials of colitis in children particularly abdominal tuberculosis in our setting, enabling treatment with anti-tuberculous therapy in such cases with often good prognosis thus sparing such children the risks of being labelled as possible cases of IBD particularly Crohn's disease and its treatment with various immunosuppressive agents and the attendant side effects as well as indirect economic costs to the child and affected families.[29]

During upper gastrointestinal endoscopy biopsies should be obtained from different sites for histological diagnosis; as even in the absence of any macroscopic findings on endoscopy, important diagnoses have been made from tissue biopsies obtained from normal appearing parts of the gut, thus enabling either a modification or change of patient's management for the better in such circumstances. In a study by Thakkar and colleagues[30] the overall rate of change of management after endoscopic evaluation in children with IBD was 42% necessitating addition of a new medication as the most common intervention.

In parallel to the growth of paediatric gastroenterology sub-speciality, gastroenterological disorders requiring endoscopy for diagnosis, therapy and surveillance/follow -up have shown a rising incidence globally. With the development of fibre-optic endoscope, gastrointestinal endoscopy has become a revolutionary diagnostic as well as therapeutic tool. Endoscopy has shown superiority in terms of diagnostic yield over earlier methods of diagnosing common as well as rare gastrointestinal disorders.[31]

A gap in knowledge exists on gastrointestinal endoscopy practice in children in the sub-Saharan Africa with limited data reported mostly by adult gastroenterologists in Zambia, Sudan, and Nigeria.[32, 33,34] There has been a rapid increase in the need for upper and lower gastrointestinal endoscopy in children in our setting where key health focus is skewed towards prevention and control of endemic infectious diseases.

Hence, the objectives of the study were to determine the socio-demographic characteristics; presenting symptoms; indications; diagnostic yields; impact on management; complications and to design algorithms for medical indications of gastrointestinal endoscopy in children.

1.2 Ethical Consideration

All study data collection tools used to collect relevant subjects information from medical records, Division of Gastroenterology and Histopathological Laboratory databases were stored in a well secured locker. Retrieved subjects' data were subsequently transferred to electronic data and stored in a pass worded secured database.

All data set used for the study analysis were void of any patient's identifying information and the participant's folder identified by the assigned study number to maintain anonymity.

The list containing subject's names and study numbers were stored separately from the data collection tools. The data set was subsequently reviewed and cleaned up to ensure absence of coding errors prior to the statistical analysis.

Potential risks: This was a retrospective review of medical records with anonymity. There were no direct contact with subjects and hence no human risks or harms were anticipated in the current study and individual informed consent was waived.

Potential benefits: Results from this study will help to improve medical gastrointestinal endoscopy service in children in our setting. Feedback from the study results will guide appropriate selection of children needing gastrointestinal endoscopy with improvement of impact of endoscopy in management of children with various gastrointestinal disorders.

Data from this study will be presented at 52nd Annual General Meeting of ESPGHAN in Scotland in 2019 and will be submitted for publication in an international journal with Thomson Reuters impact factor.

Ethical approval: Study ethical approval was obtained from the University of Cape Town, Faculty of Health Science Human Research Ethics Committee (HREC REF: 089/2017) and written permission from the Red Cross War Memorial Children's Hospital Research Committee and Management prior to the commencement of the study.

1.3 Chosen journal for publication

The Journal of Pediatric Gastroenterology and Nutrition (JPGN) was chosen for possible publication of this research. JPGN is the official journal of the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and the North American Society of Pediatric Gastroenterology Hepatology and Nutrition (NISPGHAN). Both societies are the leading organizations in the field globally with eminent scholars in the field publishing best practice guidelines. JPGN is a peer reviewed medical journal with wide scope covering medical research in paediatric gastroenterology, hepatology and nutrition.

The current study to the knowledge of the researchers is the first comprehensive review of medical gastrointestinal endoscopy in children in the sub- Saharan African region undertaken by paediatric gastroenterologists and their trainees and will serve as a base for future research on the subject not only in our setting but also globally.

This paper has been formatted according to the author's guidelines of the Journal of Paediatric Gastroenterology Hepatology and Nutrition (See attached appendices).

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CHAPTER 2: PUBLICATION – READY MANUSCRIPT

TITLE:

Medical Gastrointestinal Endoscopy in Children: Experience in a Tertiary Paediatric Hospital in Cape Town, South Africa

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ABSTRACT

Background: Endoscopy is an important diagnostic, therapeutic and surveillance modes of management in children with gastrointestinal disorders.

The objectives of the study were to determine the sociodemographic characteristics, presenting symptoms, indications; diagnostic yields, management impact, safety/complications and design algorithms for the medical indications of gastrointestinal endoscopy in children.

Methods: This was a cross sectional descriptive study in children <18years who underwent gastrointestinal endoscopy (2007 – 2016).

Ethical approval was obtained from University of Cape Town.

Datasheet was used in retrieving relevant patients' variables from the hospital medical records and Division of Paediatric Gastroenterology endoscopy and laboratory databases. Data was analysed using Stata 13.1. A p- value of less than 0.05 was considered statistically significant.

Results:

A total of 402 children underwent 773 endoscopies: 670 were oesophagogastroduodenoscopy (OGD), 103 colonoscopies with 78(10.1%) being combined OGD/colonoscopy procedures.

Main diagnostic indications for OGD, combined OGD/colonoscopy and colonoscopy alone respectively were chronic abdominal pain 51 (12.6%), probable inflammatory bowel disease (IBD) 30(7.5%) and IBD 30(7.5%).

Change 143(35.6%)/insertion 87(21.6%) of percutaneous endoscopic gastrostomy and polypectomy 8 (2.7%) were the most common therapeutic indications for OGD and colonoscopy respectively.

The overall diagnostic yield was 64.8% (116/179) for OGD and 62.7% (42/67) for colonoscopy respectively. Significant endoscopic impact 298(74.1%) on patients management was observed ($p<0.001$) while complications occurred in 4.0% (16).

Conclusion:

Significant endoscopy yields and impact on patient's management with low complication rate were observed.

Use of standard guidelines to ensure selection of patients with appropriate indications for endoscopy should be encouraged for significant impact on management.

Key Words: Gastrointestinal endoscopy; indications; diagnostic yields; therapy; impact on management; Complications

What is known?	Technological advancements in endoscopy design and its devices have led to the evolution of paediatric gastrointestinal endoscopy with increasing use in diagnostic, therapeutic and surveillance modes of management.
What is new?	-Gastrointestinal endoscopy procedures may not add to patients management if clear indications are not present and the procedures should therefore be performed only in clinical conditions in which it has shown superiority over other diagnostic methods. -Appropriate selection of cases with clear indications will result in high diagnostic yields that will impact on patient's management. -Eosinophilic oesophagitis (EoE), Coeliac disease and inflammatory bowel diseases are not common in our setting.

INTRODUCTION

Paediatric endoscopy has evolved to become an important diagnostic, therapeutic and surveillance modes of management in children with various gastrointestinal disorders[1,2] owing to the technological advancements in endoscopy design and its devices.[3,4]

Improvements in sedation, anaesthesia[4] and skills in monitoring of vital signs of patients,[5] during endoscopic procedures have added to the increased and safe use of gastrointestinal endoscopy in children and neonates.[5,6,7]

Indications for gastrointestinal endoscopy are diverse and fundamental to the assessment, treatment, and follow- up/surveillance of children with gastrointestinal disorders[8] with high diagnostic and therapeutic yields and should be performed in clinical conditions in which it has shown superiority over other diagnostic modalities.[8]

Biopsy results from endoscopies have improved the diagnosis of some gastrointestinal diseases as diagnoses could be made from histopathological examinations of tissue biopsies obtained from both macroscopically normal and abnormal looking tissues on endoscopy. [9]

The sensitivity of endoscopic examinations varies with the age of the child and indication for the oesophagogastroduodenoscopy (OGD) and colonoscopy procedures respectively. [10,11]

Several published societal guidelines exist for the performance of gastrointestinal endoscopy in children[12,13,14] which recommended that there should be its clear indications such that the findings could impact on management.

There is paucity of data on paediatric gastrointestinal endoscopy in sub- Saharan African region with most studies jointly reported with adult gastroenterologists.[15,16,17]
The objectives of the study were to assess the sociodemographic characteristics, presenting symptoms, indications, endoscopic yields, management impact, complications and design algorithms for the medical indications of gastrointestinal endoscopy in children.

PATIENTS AND METHODS

Study setting:

This study was conducted at Red Cross War Memorial Children's Hospital (RCWMCH) which is a tertiary paediatric hospital affiliated to the University of Cape Town, in Cape Town, South Africa.

All gastrointestinal endoscopies in children in the hospital were done following standard protocols and under general anaesthesia by either consultant paediatric gastroenterologists, a paediatric surgeon or trainee paediatric gastroenterology fellows under supervision.

Routine diagnostic, therapeutic and surveillance endoscopies are done in the unit. For all diagnostic gastrointestinal endoscopies done, multiple mucosal biopsies were taken from different parts of the gastrointestinal tract as follows: upper gastrointestinal tract – oesophagus (upper, mid and lower), stomach (body and antrum), and duodenum (first and second parts); lower gastrointestinal tract (rectum, sigmoid, descending, transverse, ascending colon, caecum, and terminal ileum). Biopsies were procured from both normal and abnormal appearing mucosa of the gastrointestinal organs for diagnosis.

Histological diagnosis of mucosal disease was made by a well experienced pathologist.

Study design

It was a retrospective cross sectional descriptive study undertaken among children and adolescents who underwent gastrointestinal endoscopy in RCWMCH from 1st January, 2007 to 31st December, 2016.

Study population

This comprised all children and adolescents who underwent upper and lower gastrointestinal endoscopy in the Paediatric Gastroenterology Division during the period under review.

Sample Size determination:

Out of 415 subjects identified from the medical records 13 were excluded as 11 had missing folders while 2 had incomplete records leaving 402(96.9%) children with complete records to be studied.

Inclusion criteria

All children who had medical gastrointestinal (oesophagogastroduodenoscopy and/or colonoscopy) endoscopy from 1st January, 2007 to 31st December, 2016 with complete medical records were studied.

Exclusion criteria:

Subjects with missing folders, incomplete folders and/ or medical records documented.

Permission for the Study:

Study ethical approval was obtained from the University of Cape Town (UCT), Faculty of Health Science Human Research Ethics Committee (HREC REF: 089/2017) while written permission was obtained from the RCWMCH Research Committee and Management prior to the commencement of the study (See Appendices).

Study Datasheet:

Data was collected using datasheet designed for the study from the medical records of subjects identified by Clinicom (a clinical software for entering diagnosis in the republic of South Africa health System) search using the current ICD10 codes (1552; 1553;1587; 1588;1653;1589;1591; 1653;1597) for medical gastrointestinal endoscopic procedures. Data sheets were used in retrieving other relevant variables of patients from the Division of Paediatric Gastroenterology endoscopy and laboratory (histopathology) databases respectively during the period under review.

Relevant information were retrieved from the medical records of each patient including sociodemographic characteristics, initial presenting symptoms, type of gastrointestinal endoscopy performed (OGD, OGD with colonoscopy or colonoscopy alone) with specific indication/s, macroscopic findings on endoscopy, complication/s following endoscopy, histological diagnosis, and any change in management post endoscopic procedure were obtained.

Diagnostic yield of endoscopy in the current study were classified as either positive (presence of any macroscopic endoscopic or histologic abnormality found excluding mild inflammation on histology) or negative (no or minor abnormality/normal his tology) effecting a positive contribution.[18, 19]

Mild inflammation reported on histology was not regarded a positive histologic outcome as the clinical significance of isolated mild histologic findings is inconclusive. [18, 19]

The endoscopic procedures were further subdivided into 2 categories: a positive contributive impact (the procedure had a positive impact on diagnostic and/or therapeutic modalities) and non- contributive impact (a procedure with no diagnostic or therapeutic effect).

In our centre, RCWMCH, cases of foreign body and caustic ingestions as well as laparoscopic insertion of percutaneous gastrostomy tube are undertaken by the paediatric surgical team on separate endoscopy lists while the paediatric gastroenterology unit undertakes the medical endoscopy cases mainly for diagnostic OGD and colonoscopy as well as therapeutic indications of gastrointestinal endoscopy(insertion/change of percutaneous gastrostomy tube, banding or sclerotherapy for oesophageal/gastric varices, polypectomy) among others

Socioeconomic class determination:

Patients were classified as low, middle, or high socioeconomic class according to their gross income per annum for the purposes of service fee determination.

Low income: H0- social grants(fully subsidized) or H1: (<70, 000R (4800USD)/annum for individual or single or less than R100,000(6900USD) for household/family unit), middle income, H2- (equal to or more than R70, 000 (4800USD) but < R250, 000 (17,300USD)/annum for individual/single or equal to or more than R100,000 (4800USD) but less than R 350,000 (24,200USD) for household/family unit), and high income, H3 (equal to or >R250, 000 (17,300USD)/annum for individual/single, or equal to or more than R350, 000 (24,200USD)/annum household/family unit) respectively.[20]

The socioeconomic distribution of patients studied was adapted using the uniform fee schedule regulations for health care services rendered by the Western Cape Department of Health South Africa, 2017, [18] as the study was conducted at Red Cross War Memorial Children's Hospital, Cape Town, which is a public hospital in the Western Cape Province.[20]

Data Analysis:

Data was captured in Microsoft Excel spread and exported to Stata 13.1 for statistical analysis. Categorical variables were presented as frequency tables, and numerical variables as descriptive measures, expressed as median and range.

The association between categorical variables was assessed using Pearson chi- square test and student t- test where appropriate.

Endoscopy diagnostic yield was calculated for initial examination involving diagnostic indications for upper and lower endoscopy respectively and change in and contribution to management was assessed.

Algorithms of the indications for upper and lower endoscopy in children were subsequently designed using the results obtained from the study. A p- value of less than 0.05 was considered statistically significant.

Results

Study subjects characteristics:

Four hundred and two patients were studied. Females were 220(54.7%) with a male to female ratio of 0.8: 1. Their median age was 5.5 (range: 0.1 – 18) years with majority 394 (98.0%) being younger than 13years old and of normal weight 276 (68.6%) while most were of low socioeconomic class, 307(76.4%) (Table 1).

Endoscopic procedures:

A total of 773 gastrointestinal endoscopies were undertaken. Total OGD done was 670 (86.7%) out of which 592(76.6%) and 78(10.1%) respectively were OGD alone and OGD combined with colonoscopy. One hundred and three colonoscopies with 78 (10.1%) being combined OGD/colonoscopy and colonoscopy alone 25(3.2%) were also performed (Table 1). The median OGD and colonoscopy performed per patient was 1 (range 1 to 12) and (1 to 4) respectively.

Presenting symptoms among subjects:

The presenting symptoms for OGD, combined OGD/colonoscopy and colonoscopy alone were as shown in Figure 1a, 1b, and 1c respectively. Feeding difficulty/poor feeding 102 (25.4%), poor weight gain/failure to thrive/loss of weight 100 (24.9%), upper gastrointestinal bleeding 81 (20.1%), and recurrent aspiration/silent aspiration 76(18.9%) were the most common presenting symptoms in children undergoing OGD.

Among patients that had combined OGD with colonoscopy the most common presenting symptoms were chronic abdominal pain 27 (6.7%), chronic bloody loose stools 16 (4.0%), and chronic diarrhoea 15(3.7%).

Also in patients who underwent only colonoscopy the most common presenting symptoms were rectal bleeding 11(2.7%) and chronic bloody loose stools 7(1.7%).

Indications for endoscopy:

Among 670 OGD performed 179 (26.7%), 287(42.8%), 204 (30.4%) were respectively for diagnostic, therapeutic and follow – up/surveillances indications.

Among 103 colonoscopy undertaken 67 (65.0%), 30 (29.1%), 6 (5.8%) were for diagnostic, follow-up/surveillance, and therapeutic indications respectively.

The main diagnostic indications for OGD were: chronic abdominal pain, 51(12.6%), gastro-oesophageal reflux 30 (7.5%), probable eosinophilic oesophagitis (EoE) 17 (4.2%), chronic diarrhoea 17 (4.2%), coeliac disease 9(2.2%), food allergy 6 (1.5%), aspiration 5 (1.2%) among others while the therapeutic indications for OGD included: insertion of percutaneous gastroscopy (PEG) tube 87 (21.6%), change of PEG 143 (35.6%); sclerotherapy 29 (7.2%) and variceal band ligation 28 (7.0%) for various causes of upper gastrointestinal bleeding/portal hypertension.
The follow – up/surveillance indications for OGD were mainly for previous upper gastrointestinal bleeding secondary to oesophageal varices 204(50.7%).

The major diagnostic indications for combined OGD and colonoscopy were inflammatory bowel disease, IBD 30 (7.5%), chronic diarrhoea 12 (3.0%), abdominal tuberculosis 10 (2.5%), chronic abdominal pain 10 (2.5%), chronic iron deficiency anaemia 6 (1.5%), IBD screening in those with autoimmune hepatitis 3 (0.7%), protein losing enteropathy 2 (0.5%) while follow up/surveillance indications were mainly for inflammatory bowel disease 2 (0.5%).

Diagnostic indications of colonoscopy were IBD 30 (7.5%), lower gastrointestinal bleeding 26(6.5%), abdominal tuberculosis 9 (2.2%), bloody diarrhoea 2(0.5%) while the therapeutic colonoscopy indications were for polypectomy 6 (100.0). Also 30 (7.5%) cases were for IBD follow -up/surveillance (Table 2).

Terminal ileum intubation and caecal examination rate:
Among 103 colonoscopies done, successful terminal ileum intubation and caecal examination rate was achieved in 95 (92.2%) cases. Five (4.9%) cases were procto-sigmoidoscopies for follow up of IBD while 3(2.9%) had failed terminal ileum intubation (Table 1).

Diagnostic yields:
Abnormal (positive) macroscopic findings on endoscopy were reported on 79/179(44.1%), 35/68(51.55%), and 46/67(53.7%) of OGD, combined OGD with lower endoscopy, and colonoscopy alone respectively.

Upper gastrointestinal bleeding showed the highest percentage 72.1%(31/43) on abnormal endoscopic (OGD) findings.

Also, positive histological findings on OGD, combined OGD with colonoscopy, and colonoscopy alone were 62/179(34.6%), 34/68(50.0%), and 32/67(47.8%) respectively. See Table 3.

The overall normal endoscopic findings (both macroscopic findings on endoscopy and histological findings) were 63/179(35.3%) and 25/67(37.3%) for OGD and colonoscopy (see Table 3) while overall diagnostic (endoscopic) yield was 116/179(64.8%) for OGD and 42/67(62.7%) for colonoscopy respectively which were significantly high.

As depicted in figure 2, the OGD endoscopic yield reported gastritis in 50(27.9%), and oesophageal varices 31(17.3%) while inflammatory bowel disease (Crohn's disease 9(13.4%), ulcerative colitis 7(10.4%), juvenile polyps 9(13.4%) and intestinal tuberculosis 7(10.4%) were observed on colonoscopy respectively.

On test of association between the macroscopic endoscopic findings to histological findings, significant statistical association was observed in some OGD diagnostic variables including chronic abdominal pain ($p = 0.026$) and upper gastrointestinal bleeding ($p = <0.001$). Other variables in both OGD and lower scope did not show any significant statistical relationship ($p>0.05$). See Table 3 (Supplementary Digital Content)

The relationship between the different sociodemographic characteristics and OGD diagnostic yields were not statistically significant: age ($p = 0.197$), sex ($p= 0.403$), and socioeconomic class ($p= 0.400$). Similarly no significant statistical relationship was observed between the different sociodemographic characteristics and colonoscopy diagnostic yield: age ($p = 0.774$), sex ($p= 0.248$), and socioeconomic class ($p= 0.440$) respectively.

Percutaneous endoscopic gastrostomy insertion/change:

A total of 230 PEG procedures were undertaken comprising 143(62.2%) change of PEG to gastrostomy tubes and 87 (37.8%) PEG insertions. The indications for PEG insertion included feeding in children with neurological deficits particularly cerebral palsy, traumatic brain injury, prolonged unconsciousness with unsafe swallowing, silent

aspiration or FTT/poor weight gain, difficulty/inco-ordinate swallowing and for medication adherence in patients with acquired immune deficiency syndrome.

Among patients who underwent endoscopy for PEG insertion, there was significant increase in weight upon their feeding via gastrostomy tubes among affected patients. From the study the median weight for age z-scores pre- PEG insertion among affected patients was -2 (range: -3 to +1) which increased to 0 (-1 to +2) at the time of change of PEG to gastrostomy tubes (and the difference was statistically significant ($p < 0.001$). The PEG were changed to a gastrostomy tube after a mean period of 3.7(range 3.0- 12.0) months with 2 (1.4%) patients changed to a Mickey type of gastrostomy tube.

Impact of gastrointestinal endoscopy on management:

All the endoscopies including OGD, OGD/colonoscopy and colonoscopy alone (diagnostic/therapeutic/surveillance) done showed a positive impact on the management of 298 (74.1%) patients ($p < 0.001$).

The impact of endoscopy on the management reported included feeding via inserted PEG tube 141 (47.3%), addition of new medication/s 70 (23.5%), treatment of varices using either sclerotherapy 29 (9.7%) or band ligation 28 (9.4), polypectomy 8 (2.7), therapy for eradication of Helicobacter pylori associated gastritis 8 (2.7%), change of medication/s for different gastrointestinal conditions 6 (2.0), nutritional therapy using exclusive enteral nutrition for Crohn's disease/minimal fat diet 5 (1.7%), or PEG insertion for medications adherence for patients on highly active anti- retroviral therapy 2(0.7%).

There was no change in treatment in 104(25.9%) of patients.

Safety/Complications:

The majority 386(96.0%) of cases had no complications/safety concerns following endoscopy. Complications occurred in 16 (4.0%) patients. The major complications were anaesthetic related or following PEG insertion: bradycardia/hypotension 2 (0.5%), failed extubation 1 (0.2%), de- saturation 1 (0.2%), pneumo- peritoneum 1 (0.2%), stridulous breathing on extubation 1(0.2%), or retained/ buried bumper following PEG insertion (n= 1 (0.2%)) while minor complications included: pulling out/falling- off of gastrostomy tube 7(1.7%), PEG skin site infections 1(0.2%), over- granulation tissue formation following PEG insertion 1 (0.2%). No mortalities were observed among the patients.

The algorithms for the various indications for performing OGD, combined OGD with colonoscopy and colonoscopy alone among patients were designed using the observed results (Supplemental Digital Contents -Tables 2 to 5).

Discussion

Paediatric gastrointestinal endoscopy has advanced in the last few decades allowing a greater understanding of various gastrointestinal disorders, and becoming an invaluable modality in diagnosis, therapy, follow-up/surveillance of most gastrointestinal diseases.[2,13] The current study is the first most comprehensive report of paediatric gastrointestinal endoscopy undertaken by paediatric gastroenterologists and trainees in the sub-Saharan African region. [21,22,23]

The median age of the patients in the present study was 5.5 (range: 1 month to 18) years which is comparable to findings in similar studies.[23, 24] Most of the patients in the current study were young with only 2.0%(8) of them being older than 13years. This is a paediatric study bias as the hospital does not accommodate patients over 13years.

Various sociodemographic characteristics including age, sex, socioeconomic class did not significantly influence the positivity of diagnostic yields both for OGD and colonoscopy, unlike in a similar study[18] where age was a determinant factor. From the study most of the patients were females and of low socioeconomic background. However social class and gender distribution of patients did not significantly influence the endoscopic yield.

Studies have shown significant association between incidence and outcome of common gastrointestinal conditions including coeliac disease and assessing endoscopy services with socioeconomic class of patients as cost implications could be a limiting factor in management.[25,26]

In our setting majority of the patients enjoyed government subsidized medical care either wholly or in part and so most of the patients though of low socioeconomic class had equal access to standard medical care, [20] including gastrointestinal endoscopy.

However, Akbulut and co- workers[27] as well as Vazou et al [28] corroborated the finding in the current study that gender has no effect on the diagnostic yield in children with chronic abdominal pain and type 1 diabetes undergoing upper endoscopy.

Abdominal pain has been reported as the most common indication for OGD in most similar studies.[16, 19] This was corroborated in the diagnostic indications of OGD in the present study.

In addition feeding difficulty/poor feeding with poor weight gain/failure to thrive (FTT) were the most prevalent indications for performing therapeutic OGD in the current study. In our centre therapeutic upper endoscopy mainly for insertion/change of PEG for

feeding, or for medications to maintain drug adherence in children with AIDS and having inco-ordinate swallowing were routinely carried out.

Rectal bleeding and chronic bloody loose stools were the two leading indications for colonoscopy in the present study which is similar to findings by other workers.[29, 30]

Chronic abdominal pain was the most common diagnostic indication while insertion/or change of PEG and sclerotherapy/or band ligation for oesophageal varices were the two leading indications for therapeutic OGD. This experience in the current study corroborates the recommendations by key expert societal guidelines on indications for performing endoscopy in paediatric age range.[13]
Combined OGD and colonoscopy have been recommended for the diagnoses and follow-up of some paediatric gastrointestinal disorders including IBD, polyposis, and chronic diarrhoea [31, 32] as in the current study.

Most paediatric gastrointestinal disorders present with different symptoms and signs and often definitive diagnoses are not made explicit as combined presenting symptoms and signs are used for various presumptive clinical diagnoses as in the present study. [8, 13, 31]

Identification of caecal landmarks including the opening of the appendix during colonoscopy has been shown as the gold standard for its completeness. It is invaluable in the diagnosis of some gastrointestinal disorders including IBD, intestinal tuberculosis, chronic diarrhoea among others. [33, 34] Terminal ileum intubation rate of 92.2% was observed in the current study which is higher than findings in similar studies [33, 34] The high caecal examination and terminal ileum intubation rate in the present study could be as a result of adequate bowel preparation, use of general anesthesia and experience of the paediatric gastroenterologists allowing higher colonoscopy endoscopic yield and therapy.

The overall endoscopic yield for upper and lower endoscopy in the present study was significantly high. High diagnostic yields have equally been reported for OGD and colonoscopy in similar studies[18,19, 35,36] The high endoscopic yield observed in the present study could be due to appropriate selection of cases for endoscopy using standard societal guidelines,[37] pre- procedure preparations including bowel

preparations as well as obtaining of biopsies at the time of endoscopy from both macroscopically normal and abnormal looking gastrointestinal mucosa.[38] The usefulness of obtaining biopsies from normal looking mucosa is known to improve diagnostic yields in paediatric gastrointestinal endoscopy.[39] Also negative histopathological findings on biopsies may be useful in excluding diagnoses thereby relieving anxiety amongst patients and families [40] as well as averting need for further investigations. However, considering the potential complications and costs of gastrointestinal endoscopy under general anaesthesia, appropriate clinical judgment should be applied in selecting patients with the right indications.[41]Some macroscopic findings on endoscopy showed significant statistical relationship with histopathological diagnosis in the present study as previously reported.[2]

There was a significant impact of gastrointestinal endoscopy in the current study. These impacts included both diagnostic and therapeutic modalities. In the present study, colonoscopy biopsies of terminal ileal pathology were important in distinguishing intestinal tuberculosis from Crohn's disease. Both Crohn's disease and intestinal tuberculosis may have similar presentations so that it is important to exclude tuberculosis before starting immunosuppressive treatment for IBD[42] as was seen in the current study.

Most children with feeding difficulty/poor weight gain mainly with neurological disorders like cerebral palsy had OGD for insertion of PEG for adequate feeding thus ensuring that their daily recommended dietary allowances are met resulting in improved growth as evidenced by their appreciable increase in median weight for age Z- scores. Similar findings have been corroborated by other workers.[43, 44, 45] Also children with poor medications adherence particularly those with HIV/AIDS having swallowing difficulties in the present study had PEG insertion, allowing regular administration of their medications thus averting development of drug resistance.[43]

Other therapeutic modalities of gastrointestinal endoscopy in the present study that impacted positively on the outcome included: sclerotherapy or band ligation for bleeding oesophageal varices or eradication of oesophageal varices in patients with biliary atresia with associated portal hypertension or extra- hepatic portal vein thrombosis and those with juvenile polyposis that had polypectomies. Similar reports have been documented by other researchers.[45, 46] Also Thakker et al[9] had reported a 42% change in

management mainly addition of new medication/s after repeat endoscopy in children with IBD thus improving their treatment outcomes similar to the current study.

No mortalities were reported in the current study similar to other studies.[47] Most of the complications in the current study were anaesthetic related and following PEG insertion as have been reported by other researchers. [45, 48, 49, 50]

Conclusion:

OGD and lower endoscopy were performed for different diagnostic, therapeutic and surveillance indications among study subjects with different presenting symptoms. A high degree of endoscopic yield of both OGD and colonoscopy were observed with significant diagnostic and therapeutic impacts on patients' management with minimal safety concerns/complications which were mainly general anaesthesia related.

Recommendation:

Use of expert societal guidelines in selecting patients with appropriate indications for gastrointestinal endoscopy will result in higher endoscopy diagnostic yields and therapeutic applications of endoscopy, positive impacts on patients' management with minimal complications.

Conflicts of interest: The authors hereby declare that we have no conflicts of interest in the manuscript, including financial, consultant, institutional and other relationships that might lead to bias.

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Table 1 : Socio- demographic and endoscopic characteristics of study subjects

Characteristic	n = 402(%)
Age (years):	
Median	5.5
Range	0.1 – 18.0
Sex:	
Male	182 (45.3)
Female	220 (54.7)
Socio economic class:	
Low	307 (76.4)
Middle	57(14.2)
High	38 (9.5)
Weight for age z- score:	
-1 < WAZ < 0 (normal)	276(68.6)
-2 < WAZ <-1 (marginal underweight)	23(5.7)
-3 < WAZ < -2 (moderately underweight)	42 (10.4)
WAZ < -3 (severely underweight)	61(15.2)
Endoscopy Performed:	
Overall oesophagogastroduodenoscopy + Colonoscopy performed	773(100.0)
Total oesophagogastroduodenoscopy	670 (86.7)
Oesophagogastroduodenoscopy alone	592(76.6)
Total Colonoscopy	103 (13.3)
Colonoscopy alone	25(3.2)
oesophagogastroduodenoscopy **+** Colonoscopy (combined procedures)	78 (10.1)
Indications for Endoscopy:	
oesophagogastroduodenoscopy (total)	670 (100.0)
Diagnostic	179 (26.7)
Therapeutic	287 (42.8)
Surveillance	204 (30.4)
Colonoscopy(total):	103 (100.0)
Diagnostic	67 (65.0)
Follow- up/Surveillance	30 (29.1)
Therapeutic	6 (5.8)
Percutaneous endoscopic gastrostomy(PEG); n= 230:	
Change of PEG	143(62.2)
Insertion of PEG	87(37.8)
Terminal ileum/Caecal intubation: (for colonoscopy, n= 103):	
Yes	95 (92.2)
No	8 (7.8)

Table 2: Indications for gastrointestinal endoscopy among study subjects

Characteristic	**N=402(%)**
A. Oesophagogastroduodenoscopy only **(N=670)**	
(i) Diagnostic (n=179)	
Chronic abdominal pain	49(12.2)
Upper Gastrointestinal bleeding/ Portal hypertension	43(10.7)
Gastro- oesophageal reflux	30 (7.5)
Probable eosinophilic oesophagitis	17 (4.2)
Chronic diarrhoea	17(4.2)
Coeliac disease	9 (2.2)
Food allergy/CMPA/FPIES♦	6(1.5)
Aspiration	5 (1.2)
Cyclical vomiting	3(0.7)
(ii) Therapeutic (n=287):	
Change of PEG	143(35.6)
Insertion of PEG	87 (21.6)
Sclerotherapy for varices with PHT	29 (7.2)
Band ligation for varices with PHT	28 (7.0)
(iii) Follow -up/Surveillance (n=204)	
Upper gastrointestinal varices	204(50.7)
B. Combined oesphagodastroduodenoscopy & colonoscopy (n=78)	
(i) Diagnostic (n=68):	
Probable inflammatory bowel disease (IBD)	30 (7.5)
Chronic diarrhoea	12 (3.0)
Abdominal tuberculosis	10(2.5)
Chronic abdominal pain	8(2.0)
Chronic iron deficiency anaemia	3 (0.7)
IBD with autoimmune hepatitis	3(0.7)
Protein losing enteropathy	2(0.5)
(ii) Follow- up/surveillance (n=10)	
Inflammatory bowel disease	10 (2.5)
C. Colonoscopy (n = 103):	
(i) Diagnostic (n=67):	
Inflammatory bowel disease	30 (7.5)
Lower gastrointestinal bleeding (rectal bleeding)	26 (6.5)
Abdominal tuberculosis	9(2.2)
Bloody diarrhoea	2(0.5)
ii. Therapeutic (n=6):	
Polypectomy	6 (100.0)
iii. Follow – up/Surveillance (n= 30):	
Inflammatory bowel disease	30(7.5)

♦FPIES: Food protein induced enterocolitis; CMPA: Cow's milk protein allergy

+Multiple entries apply in the table.

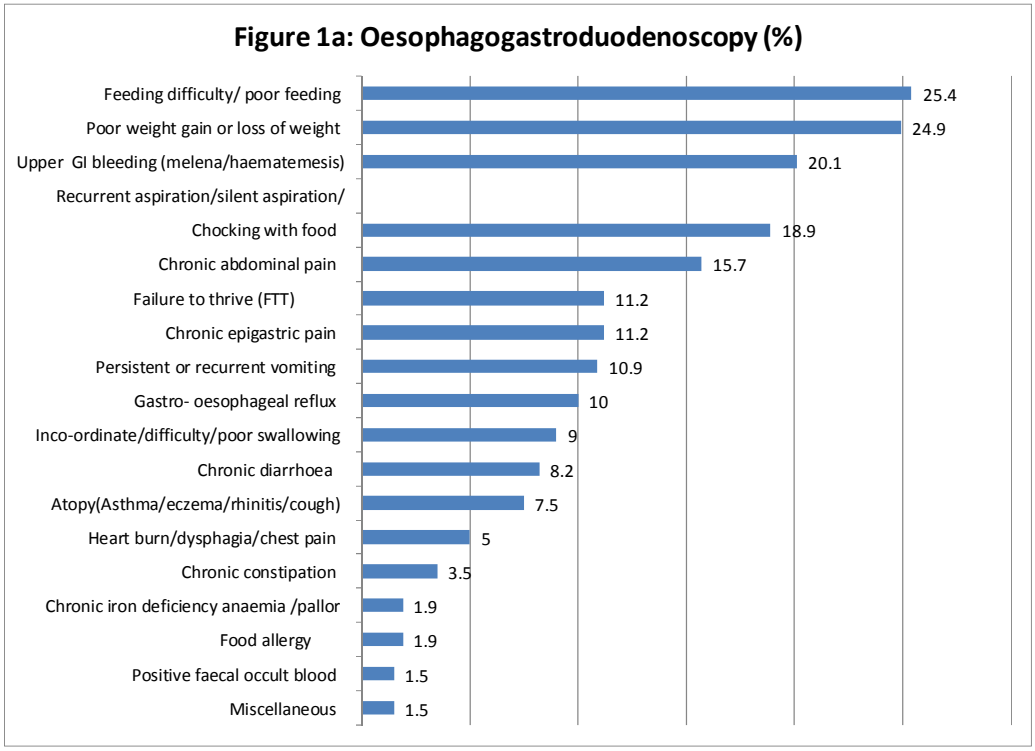


Figure 1a: Oesophagogastroduodenoscopy (%)
Feeding difficulty/ poor feeding
25.4
Poor weight gain or loss of weight
24.9
Upper GI bleeding (melena/haematemesis)
20.1
Recurrent aspiration/silent aspiration/
Chocking with food
18.9
Chronic abdominal pain
15.7
Failure to thrive (FTT)
11.2
Chronic epigastric pain
11.2
Persistent or recurrent vomiting
10.9
Gastro- oesophageal reflux
10
Inco-ordinate/difficulty/poor swallowing
9
Chronic diarrhoea
8.2
Atopy(Asthma/eczema/rhinitis/cough)
7.5
Heart burn/dysphagia/chest pain
5
Chronic constipation
3.5
Chronic iron deficiency anaemia /pallor
1.9
Food allergy
1.9
Positive faecal occult blood
1.5
Miscellaneous
1.5

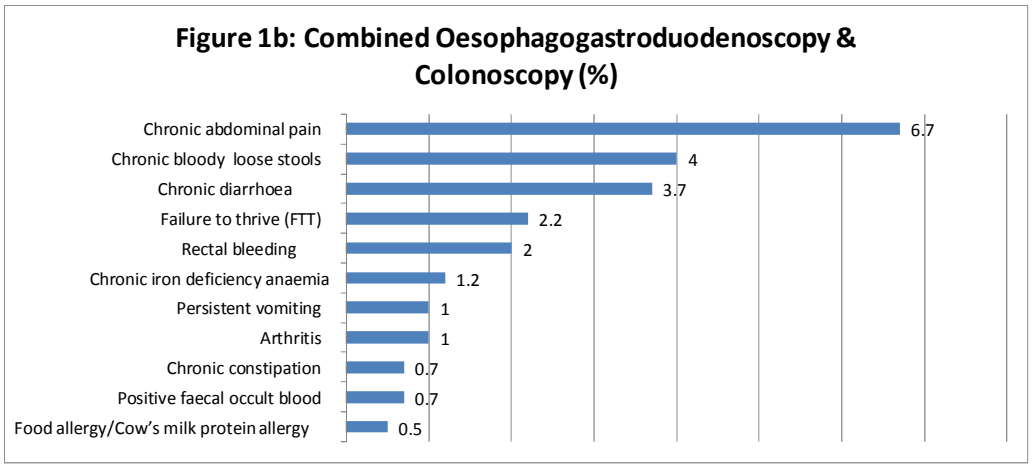


Figure 1b: Combined Oesophagogastroduodenoscopy & Colonoscopy (%)
Chronic abdominal pain
6.7
Chronic bloody loose stools
4
Chronic diarrhoea
3.7
Failure to thrive (FTT)
2.2
Rectal bleeding
2
Chronic iron deficiency anaemia
1.2
Persistent vomiting
1
Arthritis
1
Chronic constipation
0.7
Positive faecal occult blood
0.7
Food allergy/Cow's milk protein allergy
0.5

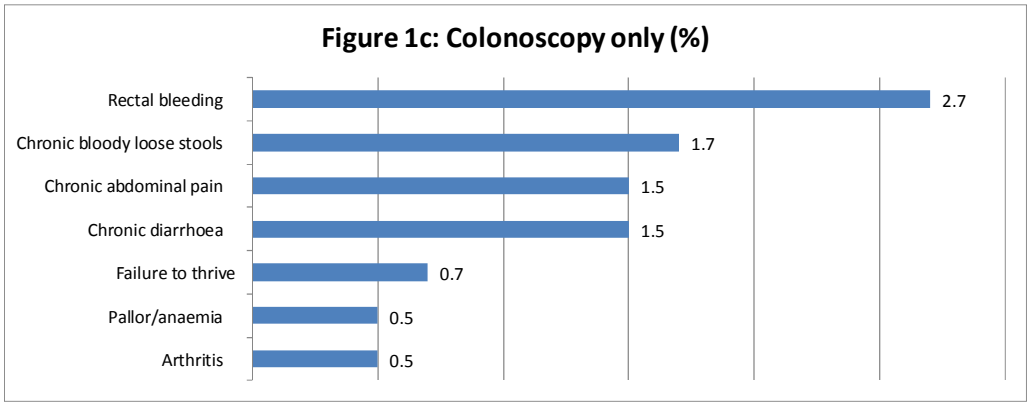


Figure 1a, b, c: Bar charts showing the presenting symptoms among patients who had oesophagogastroduodenoscopy, combined zesophagogastroduodenoscopy and colonoscopy, and colonoscopy(n= 402)
+Multiple entries apply in the table.

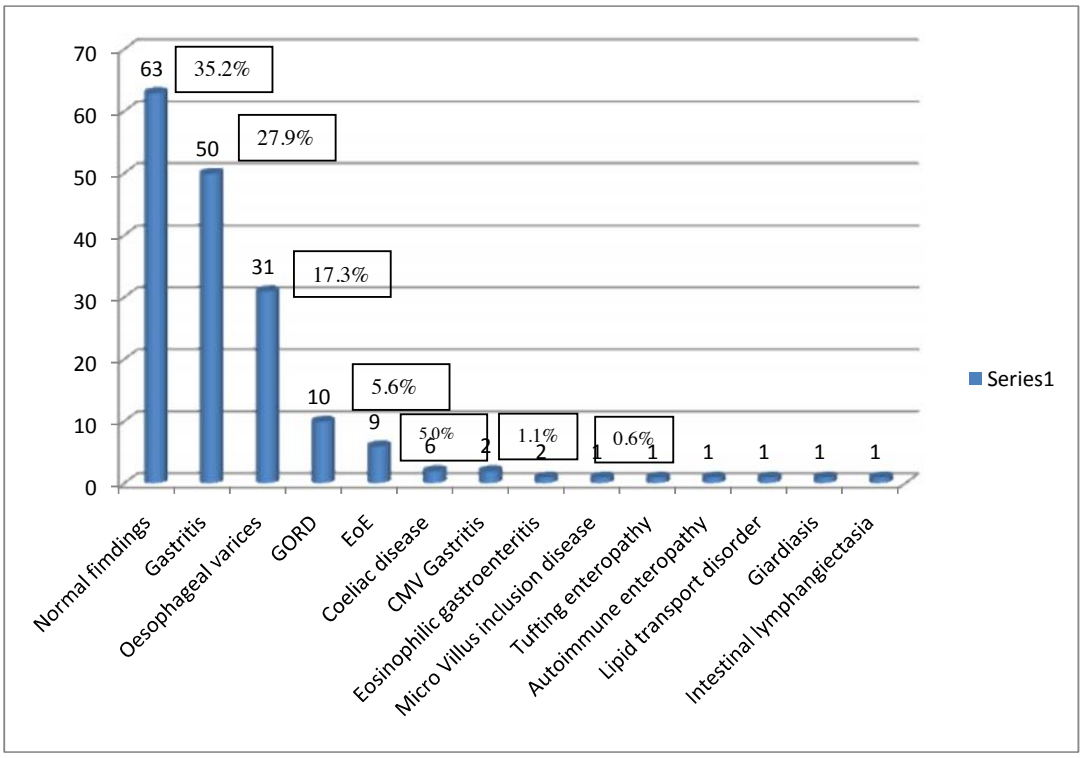


Figure 2a: Bar chart showing diagnostic endoscopic (oesophagogastroduodenoscopy) yields among subjects (n= 179).

Abbreviations: GORD- Gastro oesophageal reflux disease; EOE: Eosinophilic oesophagitis; CMV- Cytomegalo virus

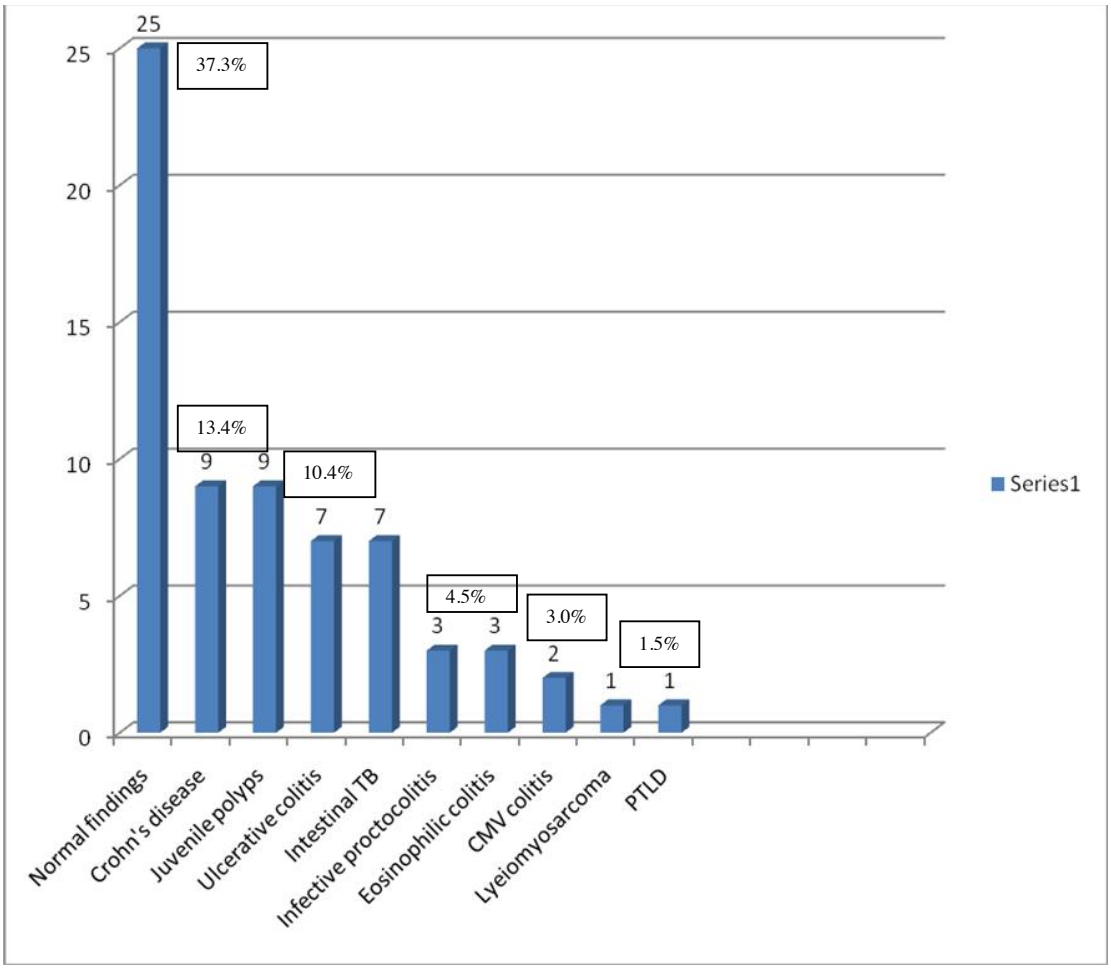


Figure 2b: Bar chart showing diagnostic endoscopic (colonoscopy) yields among subjects (n = 67).

Abbreviations: CMV- Cytomegalovirus; TB- Tuberculosis; PTLD- Post transplant lymphoproliferative disorder.

Appendix 1.1 Supplementary Digital Content;

Table 3: Relationship between macroscopic and histologic findings in children undergoing endoscopy

Indications:	Abnormal endoscopic finding	positive histological findings	p-value
a. Upper endoscopy (n=179)			
Chronic abdominal pain	20/49(40.8)	31/49(63.3)	0.026
Upper GI bleeding	31/43(72.1)	4/43(9.3)	<0.001
GORD*	8/30(26.7)	7/30(23.3)	0.766
EoE**	3/17(17.6)	3/17(17.6)	NA(1.000)
Chronic diarrhoea	11/17(64.7)	11/17(64.7)	NA(1.000)
Coeliac disease	3/9(33.3)	3/9(33.3)	NA(1.000)
Food allergy	0/9(0.0)	0/6(0.0)	NA(1.000)
Aspiration	2/5(40)	2/5(40)	NA(1.000)
Cyclical vomiting	1/7(33.3)	1/3(33.3)	0.490
Total	**79/179(44.1)**	**62/179(34.6)**	**0.066**
b. Combined upper and lower endoscopy(n= 68)			
Probable IBD****	18/30(60.0)	17/30(56.7)	0.069
Abdominal Tuberculosis	4/10(40.0)	3/10(30.0)	0.639
Chronic diarrhoea	7/12(58.3)	7/12(58.3)	NA(1.000)
Chronic abdominal pain	3/8(37.5)	3/8(37.5)	NA(1.000)
Chronic Iron deficiency anaemia	1/3(33.3)	1/3(33.3)	NA(1.000)
IBD with autoimmune hepatitis	2/3(66.7)	2/3(66.7)	NA(1.000)
Protein losing enteropathy	½(50.0)	½(50.0)	NA(1.000)
Total	**36/68(52.9)**	**34/68(50.0)**	**0.731**
c. Lower endoscopy (n=67)			
Probable IBD	19/30(63.3)	17/30(56.7)	0.598
Lower GI bleeding	12/26(84.6)	10/26(38.5)	0.575
Abdominal Tuberculosis	4/9(44.4)	4/9(44.4)	NA(1.000)
Bloody Diarrhoea	½(50.0)	½(50.0)	NA(1.000)
Total	**46/67(53.7)**	**32/67(47.8)**	**0.014**

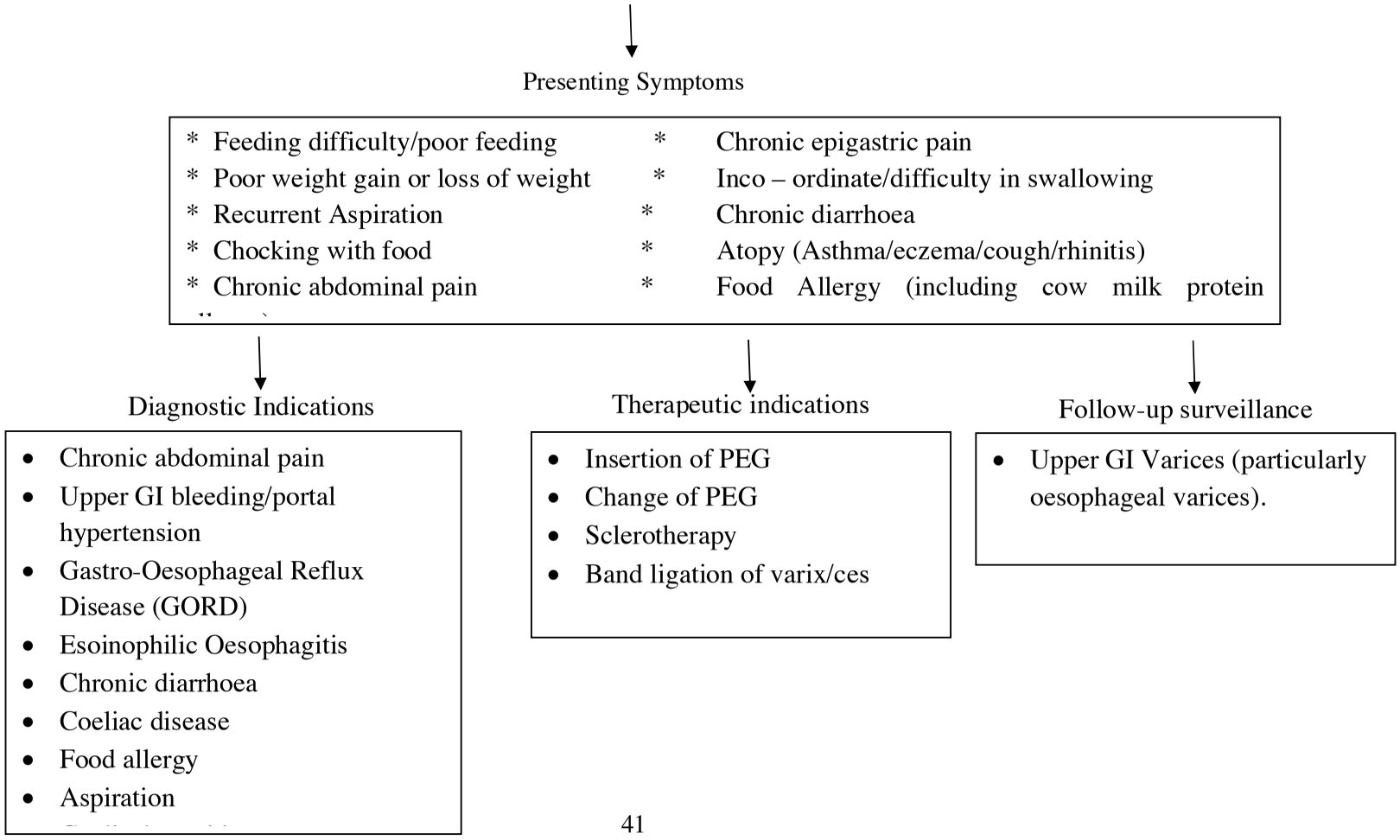
*GORD: atypical Gastro-oesophageal reflux disease, **EoE: Eosinophilic oesophagitis,

***GI: Gastro Intestinal, ****IBD: Inflammatory Bowel Disease

1.2 Appendix

Supplemental Digital Content: Table 4

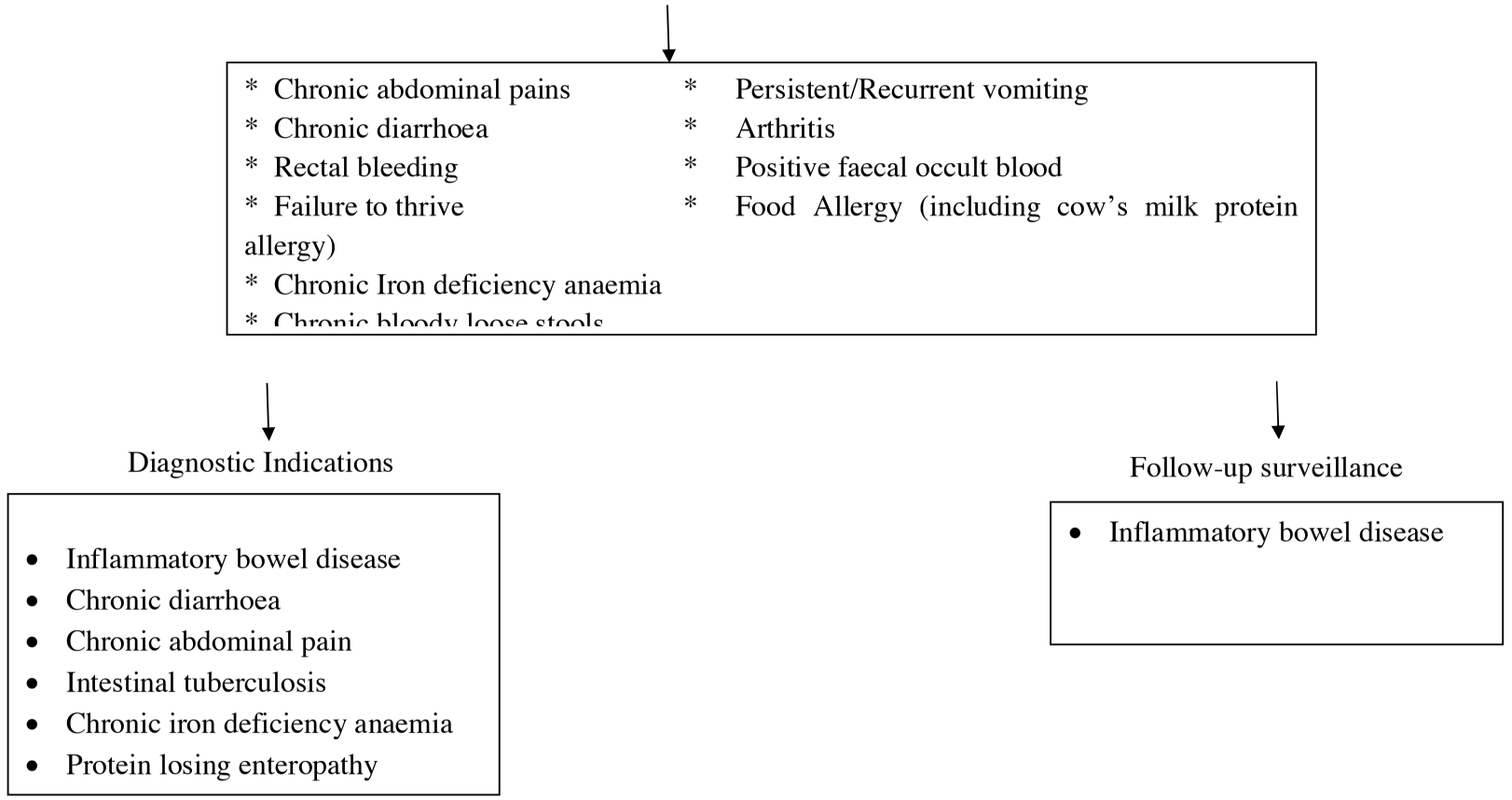
Algorithm for Medical Indicators of Oesophagogastrosduodenoscopyin Study Subjects



1.3 **Appendix**

Supplemental Digital Content: Table 5

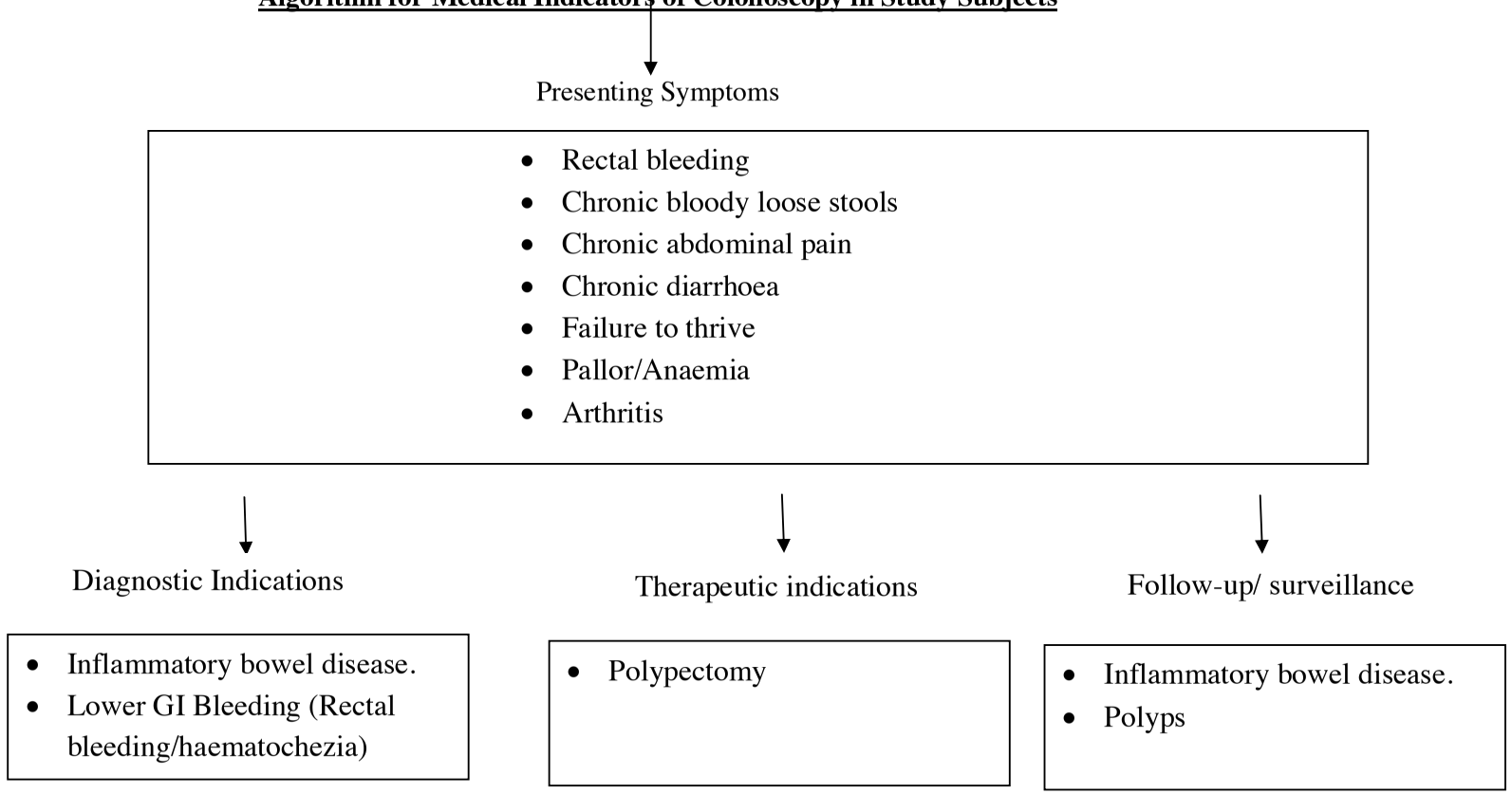
Algorithm for Medical Indicators of combined Oesophageogastroduodenoscopy and Colonoscopy in Study Subjects



1.4 **Appendix**

Supplemental Digital Content: Table 6

Algorithm for Medical Indicators of Colonoscopy in Study Subjects



1.5 Appendix

Study Data Collection Sheet

REVIEW OF MEDICAL GI-ENDOSCOPY IN CHILDREN ATTENDING RED CROSS CHILDREN'S HOSPITAL, CAPE TOWN(2007-2016)

Case Record Form Study Enrolment No.:_____

A. Socio-Demographics

Date of Birth	Age	Sex:	Male	Female
Address:	Native Language: (i) (Afrikaans (ii) English (iii) Xhosa (iv) Other (specify) _____			
Socio-Economic Class		Low Social Class (H0 and HI)	Middle (H2)	High (H3/Private)

B. Physical Examination

Anthropometry Indices:

Weight:_____kg	Height:_____cm	WFA: _____z-Score	HAZ:	BMI Z-score:	

Relevant findings on systemic examination:
(i) _____
(ii) _____

Relevant Radiological Reports (Diagnostic) Done:

(i) Plain Radiograph: (ii) Fluroscopy with speech therapy (iii) Barium Studies (iv) Milk Scan (v) CT scan (vi) MRCP

(vii) Magnetic Resonance Enterography (MRE) (viii) Others (specify): _____

C. **Clinical Characteristics:**

Primary Symptoms:

(i) Poor feeding/feeding difficulty	(ii) Poor weight gain/failure to thrive/weight loss	(iii) Bleeding per mouth/nostril/haematemesis
(iv) Lower GIB (rectal bleeding/malaena/ haematochezia	(v) Mouth ulcers	(vi) Persistent vomiting
(vii) Chronic abdominal pain	(viii) Abdominal mass	(ix) Chronic constipation
(x) Chronic Diarrhoea	(xi) Pallor/anaemia (unexplained)	(xii) Persistent fever
(xiii) Chronic abdominal cramps/bloating	(xiv) Poor appetite	(xv) Caustic ingestion
(xvi) Odynophagia/dysphagia	(xvii) Other (specify): _____	

Working diagnosis prior to endoscopy: _____

Type of Endoscopy performed:

Oesophagogastroduodenoscopy alone	Combined Oesophagogastroduodenosco and Colonoscopy	Colonoscopy alone

D. **Endoscopic Variables**:

Therapeutic Indications for Oesophagogastroduodenoscopy:

(i) PEG Insertion	(v) Oesophageal sclerotherapy
(ii) Change of PEG	(vi) Oesophageal variceal banding
(iii) PEG removal	(vii) Oesophageal non-variceal bleeding therapy (specify):
(iv) Foreign body removal	(viii) Others (specify):

Diagnostic Indications for Oesophagogastroduodenoscopy:

(i) Reflux oesophagitis	(v) Peptic ulcer disease (specify anatomic gastrointestinal site)
(ii) Coeliac disease	(vi) Helicobacter pylori infection
(iii) Eosinophilic oesophagitis (EoE)/Eosinophilic gastroenteritis	(vii) Crohn's disease
(iv) Gastri-oesophageal reflux disease (GORD)	(viii) Others (specify):

Interval between insertion and removal of PEG: (i) Time: …….. (ii) NA

Therapeutic Indications for Colonoscopy:

(i) Polypectomy	(ii) Foreign body removal	(iii) Treatment of haemorrhagic lesions	(iv) Other (specify):

Diagnostic Indications for Colonoscopy:

(i) Unexplained anaemia	(ii) Unexplained chronic diarrhea	(iii) Non-specific colitis
(iv) Unexplained abdominal pain	(v) Peri-anal lesions/Proctitis/fistula	(vi) Unexplained Failure to Thrive (FTT)
(vii) Rectal blood loss	(viii) IBD (specify type):	(ix) Abdominal Tuberculosis
(x) Allergic colitis	(xi) Cytomegalovirus (CMV) Colitis	(xii) Suspicion of graft versus host disease (GVHD)
(xiii) Polyposis syndrome	(xiv) Cancer surveillance	(xv) Surveillance for IBD
(xvi) Others (specify):	(xvii) Others (specify):	

E. **Characteristics of gastrointestinal disorders among subjects who underwent colonoscopy:**

1. Age of onset of illness requiring colonoscopy:……..2. Duration of illness prior to colonoscopy: ……..
3. Disease activity: (i) Mild (ii) Moderate (ii) Severe
4. Extent of disease: (i) Pan-colitis (ii) Left-sided lesions (iii) Other (specify): _____
5. Current use of Corticosteroids: (i) Yes (ii) No
6. Current use of Immuno-modulators (Azathioprine/6-MP): (i) Yes (ii) No
7. Current use of Calcineurin inhibitors (e.g. Tacrolimus): (i) Yes (ii) No

8. Current use of Anti-TNF –α(Infliximab/Adalimumab): (i) Yes (ii) No

9. Other immunosuppressive therapy given (specify): _____

Oesophagogastroduodenoscopy **Findings (Macroscopy):**

(i) Normal	(ii) Abnormal (specify):

Was biopsy taken during the endoscopic procedure: (i) Yes (ii) No (iii) NA

Results following endoscopic biopsy:

(i) Histology: _____ (ii) Tissue culture (specify): _____(iii) PCR (specify): _____ (iv). NA

Colonoscopy findings:

(i) Normal	(ii) Juvenile polyps	(iii) Pan-colitis	(iv) Crohn's disease
(v) Proctitis	(iv) *Angiodysplasia*	(vii) TB Colitis	(viii) Other (specify):

Final diagnosis following Endoscopy: _____

Family history of similar illness: _____

Source of endoscopic diagnosis:

(i) From histology	(ii) Biopsy (cultural)	(iii) PCR (specify):	(iv) Other (specify):

- Is there agreement between the working diagnosis and endoscopic-enabled diagnosis: (i) Yes (ii) No (iii) NA

Complications following endoscopy:

(i) Desaturation (hypoxic event)	(ii) Arrhythmia	(v) Respiratory disease (specify):	(vii) Bleeding	(ix) Cardiac arrest
(ii) pneumoperitoneum	(iv) Gut perforation	(vi) Fistula formation (specify):	(viii) Nausea/ vomiting	(x) Mortality

Other complication/s (specify): _____

Complications recorded during or after the procedure: (i) Yes (ii) No

- **Did endoscopic findings aid/impacton patient's diagnosis/Management: (i) Yes (ii) No (iii) NA**

If 'yes" to above, state the impact on management:

a. Medication change (specify new medication(: _____
b. Addition of new medication/s (specify): _____
c. Change of medication (+) nutrition (specify): _____
d. Nutritional therapy (specify): _____
e. Surgery (specify): _____
f. Other (specify): ……

Need for repeat endoscopy: (i) Yes (ii) No (iii) NA

Indication for repeat Oesophagogastroduodenoscopy/Colonoscopy

Number of Oesophagogastroduodenoscopy done (Specify): ……..

Number of colonoscopy done (Specify):……..

Findings on repeat endoscopy:

(i) Macroscopy: _____
(ii) Histology: _____
(iii) Other (specify) _____
(iv) Normal
(v) NA

Diagnosis following repeat endoscopy: (i) same as before (ii) new/change of diagnosis (iii) NA
If 'new' diagnosis, specify: _____

Treatment offered following repeat endoscopy (specify):…….

GIT Endoscopic Outcomes:

(i) Diagnosis obtained

(ii) Improved with therapeutic endoscopy

(iii) Normal findings

(iv) Complication following procedure

(v) Others (specify): ……

Miscellaneous (other significant finding/s):……..

1.6 Appendix

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-48 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

14 February 2017

HREC REF: 089/2017

Dr Liz Goddard
Division of Gastroenterology
Paediatrics & Child Health
Red Cross War Memorial Children's Hospital

Dear Dr Goddard

PROJECT TITLE: A RETROSPECTIVE REVIEW OF MEDICAL GASTROINTESTINAL ENDOSCOPY IN CHILDREN ATTENDING RED CROSS CHILDREN'S HOSPITAL, CAPE TOWN (MPHIL CANDIDATE - DR C EKE)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

[redacted]

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed [redacted] the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

[redacted]

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

The HREC acknowledge that the student, Dr Christopher Eke will also be involved in this study.

Yours sincerely

signature removed to avoid exposure online

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 089/2017

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 089/2017

1.7 Appendix

Western Cape Government
Health

Dr Jane Kawadza
Manager: Medical Services
Email: Jane.Kawadza@Westerncape.gov.za
Tel: +27 21 658 5708 fax: +27 21 658 5166
RXH: RCC60

Dr C Eke
Red Cross War Memorial Children's Hospital

Dear Dr C Eke

APPROVAL OF RESEARCH

PROJECT TITLE: A RETROSPECTIVE REVIEW OF MEDICAL GASTROINTESTINAL ENDOSCOPY IN CHILDREN ATTENDING RED CROSS CHILDREN'S HOSPITAL, CAPE TOWN

It is a pleasure to inform you that approval is hereby granted to conduct the above-mentioned study at Red Cross War Memorial Children's Hospital.

Yours sincerely,

signature removed to avoid exposure online

Dr J Kawadza
Manager: Medical Services
Date: 23.02.17

1.8 **Appendix**

Journal of Pediatric Gastroenterology and Nutrition
Online Submission and Review System

SCOPE
The *Journal of Pediatric Gastroenterology and Nutrition* publishes original articles, special reports, review articles, rapid communications, case reports, letters to the editor, short communications, and commentaries on all aspects of pediatric gastroenterology, hepatology, pancreatology, and nutrition.

The journal follows the International Committee of Medical Journal Editors' Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URM). Manuscripts must be prepared in accordance with the URM (N Engl J Med 1997;336:309-15 and updated at http://www.icmje.org/). Manuscripts not prepared according to the Instructions to Authors will be returned to the author(s) without review.

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If the parents or guardian were unable to be located for their consent, a signed statement from the Chair of the Department or from the Institutional Review Board may be accepted. The statement must read: all attempts have been exhausted in trying to contact the parents or guardian for the purpose of attaining their consent to publish the Case Report, Letter to Editor or Image/Video of the Month.

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ARTICLE TYPES
Rapid Communication: This article type allows for rapid review (within 10 days) and publication of original studies. Manuscripts considered for rapid review will be limited to reports judged to be of general scientific or public health importance. Authors submitting Rapid Communications must provide a detailed cover letter outlining the rationale for fast tracking their work. Authors must state whether the findings could alter current standards of patient care (e.g., finding efficacy or lack of efficacy of treatment), and/or if the findings suggest a novel mechanism or understanding of disease process (e.g., new susceptibility gene identification in *H pylori* organism).

Rapid Communications should contain no more than 3000 words, structured abstract with no more than 250 words and no more than four figures and tables combined (for example, a submission may include 4 figures, 1 figure and 3 tables, 4 tables, etc., but not 2 figures and 3 tables) and no more than 50 references. Submissions exceeding these parameters without justification or without a detailed cover letter explaining the rationale for a Rapid Communication will be returned to the author for correction prior to review. Extra material such as very detailed methods, tables or figures that are not needed by most readers may be submitted as Supplemental Digital Content without limitation on length (see below). Articles submitted for Rapid Communication but deemed to be more appropriate for standard submission will be returned for resubmission as an Original Article (below).

Original Articles: Original articles are full-length reports of original research. Original articles are accepted based on their scientific relevance, the originality of the work, and the priority of the work for *JPGN* and its readership. Authors should aim for accuracy, clarity, and brevity. Long introductions, repetition of data among tables, figures, and the text, and unfocused discussions should be avoided.

Original research articles should be approximately 18 double-spaced, numbered pages, including the title page, references, figures, and tables. Failure to comply with length restrictions may result in a delay in the processing of your paper. The following length targets (up to 3000 words for the text including Introduction, Methods, Results and Discussion) are recommended for Original Articles:

- Structured Abstract: maximum of 250 words
- Introduction: 1 page (about 250 words)
- Methods: 2-3 pages (up to 750-1000 words)
- Results: 2-3 pages (up to 750-1000 words)
- Discussion: 3-5 pages (up to 1000 words)
- References: limited to those critical and relevant to the manuscript (not more than 50)
- Tables and Figures: 4 total (legends limited no more than 100 words each)
- Additional/supplemental content may be submitted as "Supplemental Digital Content (SDC)", which has no space limitation (see section on SDC below).

Clinical Trials: Original Articles of studies that prospectively assign human subjects to specific intervention or comparison groups and determine the relationship between an intervention and outcome are to be submitted as "Clinical Trials". To ensure consistency with the guidelines of the Clinical Trial Registration Statement from the International Committee of Medical Journal Editors, all trials submitted to the Journal with patient enrollment commencing after January 1, 2009 must be registered in a public trials registry prior to enrollment of the first subject. The registry must incorporate free public access, and must be searchable, open to prospective registrants, and have not-for-profit management. The following information must be included in the registry: (1) unique identifying number, (2) statement of intervention(s), (3) hypothesis, definition of primary and secondary outcome measurements, eligibility criteria, target number of subjects, funding source, contact information for principal investigator, and dates of registration, start and completion. Authors should provide the URL (website address) and trial identification number on the title page of the manuscript. This information will be published with the article. The length of Clinical Trials should follow the same guidelines as the Original Articles above (Structured Abstract (no more than 250 words); text with no more than 3000 words; no more than 50 references permitted; no more than 4 Tables/Figures; SDC permitted). Clinical trial reports should comply with the Consolidated Standards of Reporting Trials (CONSORT) and the checklist should be submitted at the end of the manuscript.

Reporting Clinical Trials Conducted by Pharmaceutical Companies: Please ensure that clinical trials sponsored by pharmaceutical companies follow the guidelines on Good Publication Practice. These guidelines aim to ensure that such trials are published in a responsible and ethical manner. The guidelines cover companies' responsibility to endeavor to publish results of all studies, companies' relations with investigators, measures to prevent redundant or premature publication, methods to improve trial identification, and the role of professional medical writers.

STAndards for the Reporting of Diagnostic accuracy studies (STARD checklist): If you are reporting a study that has assessed one or more diagnostic tests you must complete the STARD Statement, and paste it onto the end of your full manuscript.

STrengthening the Reporting of OBservational studies in Epidemiology (STROBE Statement): Reports of an observational cohort, case-control, or cross-sectional study must include the relevant STROBE Checklist at the end of the manuscript. Additional information can be found on the STROBE website.

Standards for QUality Improvement Reporting Excellence (SQUIRE statement) should be applied for quality improvement (QI) projects and those involving a detailed consensus process.

Review Articles: Review articles are usually solicited by the Editorial Board. However, unsolicited reviews of exceptional interest will also be considered. Authors should contact the Editors before submitting a review to determine whether the topic and contents are appropriate for JPGN. All proposed reviews will be approved based on a submitted list of author(s) and a brief outline for the proposed review. Reviews should be balanced and unbiased. Review articles undergo peer review. While we allow some flexibility for Review Articles, authors should aim to follow the same guidelines as the Original Articles above (exception being an Unstructured Abstract of no more than 250 words): text with no more than 3000 words; no more than 50 references permitted; no more than 4 Tables/Figures; SDC permitted). Authors submitting longer Review Articles must justify the length in the cover letter.

For Systematic reviews/Meta-analyses, please follow the guidelines listed above, but please include a structured abstract of no more than 250 words. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist should be included at the end of the manuscript. Alternatively, the MOOSE checklist should be applied for meta-analyses of observational studies.

A full list and index of reporting guidelines can be found at www.equator-network.org/library/. All can be downloaded as Word documents that can then be included at the end of the manuscript.

Short Communications: This category comprises brief reports on topics relevant to the JPGN reader and preliminary reports of original studies of relevant scientific importance. Short Communications must not exceed 2000 words. Include an unstructured abstract of 150 words or less. Short Communications should contain no more than 2 tables and/or figures, and no more than 20 references are permitted.

Invited Commentary: These submissions are typically no more than 500-1000 words in length and are usually considered by invitation only. Requests to submit a commentary regarding a 'hot topic' should be made to one of the editors. Generally no more than 5-10 references, and 1 table and/or 1 figure are permitted. No abstract needed.

Topic of the Month: These submissions are typically no more than 1000-1500 words in length and are usually considered by invitation only. An unstructured abstract should be no more than 150 words. References should be limited to those critical and relevant to the manuscript. No more than 30 references and a total of 2 figures and/or tables.

Societal Papers: These submissions are coordinated by ESPGHAN and/or NASPGHAN. For more information about submitting a societal paper, please contact the ESPGHAN or NASPGHAN Consulting Editor for Societal Papers. An abstract of no more than 250 words, is optional and can be structured or unstructured.

ONLINE ONLY ARTICLE TYPES

The JPGN is transitioning to increasing the number of articles as online only. The Editors of JPGN now select some high impact and special feature articles for online only publication, particularly those with basic scientific merit. These articles appear in all electronic version of the journal in the next issue available after receipt of material required for publication. The corresponding print issue will include the article in the Table of Contents, and will publish the article abstract. Articles are typeset in standard journal format, and the corresponding author will be emailed a PDF of the article on publication. Authors will usually be informed about the decision for this modality at the time of final acceptance.

All Case Reports, Image of the Month, Video of the Month, and Letters to the Editor will be reviewed and accepted as online only content. Papers in these sections will still be assigned to an issue and listed in the issue's Table of Contents, and will appear in full on the journal website and in all electronic versions of the journal.

Case Reports (online only): Only exceptional cases will be accepted by the JPGN as case reports; thus, the report should present unique case(s) that are deemed important to the health of our patients or the advancement of the knowledge base in our field. It is helpful if you submit a Case Report to please include in your cover letter a brief paragraph that explains why your case meets the above criteria. Alternately, you may submit your report as a Letter to Editor; Letters may include up to one figure or table.

Case Reports will be considered for publication only if they concern a hitherto unrecognized condition or offer new insight into the pathophysiology, diagnosis, or treatment of a disease. Patients should always be referred to as "the patient"; initials or other identification should not be used. Case Reports must not exceed 1,000 words, and may include up to three tables and/or figures, and no more than 8 references. An abstract is not required, and if present, it will be included in the word count.

Image of the Month (online only): Submissions for the "Image of the Month" should include one (at most two) high quality TIF endoscopic, histologic, radiologic, or photographic images of unusual or informative findings. A brief description of no more than 200 words should accompany the images. No more than 8 references permitted. No abstract.

Video of the Month (online only): Submissions for the "Video of the Month" should include high quality endoscopic video of unusual or informative findings. One or two additional associated photos, such as radiologic, pathologic, or photographic images, can also be submitted for online publication. A brief description of no more than 200 words should accompany the video. No more than 8 references permitted. No abstract. Videos should be uploaded as Supplemental Digital Content with one of the following file extensions: .wmv, .mov, .qt, .mpg, .mpeg, .mp4; and formatted with a 320 x 240 pixel minimum screen size. For more information, please review Wolters Kluwer's requirements for submitting supplemental digital content: http://links.lww.com/A142.

Letters to the Editor (online only): A Letter to the Editor may be in response to an article published in *JPGN* or may comment on a controversial issue. Letters should be brief (no more than 250 words), and will be published at the discretion of the editor. No abstract.

Filler material (in print only): Material such as historical vignettes, photographs, or brief poems/stories/comments may be submitted as 'filler' material that are inserted by the publisher into extra space as available. "Filler" space is available when a paper does not fill at least 50% of the last page in the proofs of the paper. "Fillers" are accepted at the discretion of the Editors in Chief. table

Summary of Article Type Parameters

Article Type	Abstract	What is New/ What is Known	Text Limit	Figure/Table Limit	Reference Limit
Rapid Communication	Structured 250 words	Yes	3000 words	4	50
Original Articles	Structured 250 words	Yes	3000 words	4	50
Clinical Trials	Structured 250 words	Yes	3000 words	4	50
Systematic reviews / Meta-analyses	Structured 250 words	Yes	3000 words	4	50
Review Articles	Unstructured 250 words	Yes	3000 words	4	50
Short Communications	Unstructured 150 words	Yes	2000 words	2	20
Invited Commentary	None	Not required	1000 words	1	10
Topic of the Month	Unstructured 150 words	Yes (for social media only)	1500 words	2	30
Societal Papers	Optional 250 words	Yes (for social media only)	n/a	n/a	n/a
Online Only Article Types					
Case Reports*	None	Not required	1000 words	3	8
Image of the	None	Not required	200	2	8

Month			words		
Video of the Month	None	Not required	200 words	2	8
Letters to the Editor and Response	None	Not required	250 words	1	8

MANUSCRIPT PREPARATION

Manuscripts that do not adhere to the preceding guidelines and following instructions will be returned to the corresponding author for technical revision before undergoing peer review. Concise, clearly written articles are more likely to be accepted for publication in the *Journal of Pediatric Gastroenterology and Nutrition*. Authors whose first language is not English are STRONGLY encouraged to ask a native English-speaking colleague or a professional author's editor, preferably with knowledge in the subject matter contained in the manuscript, to edit their manuscript before submission. A list of editing services is available at http://journals.lww.com/jpgn/_layouts/1033/oaks.journals/editservices.aspx.

Cover Letter: In the cover letter provide a statement as to whether the paper was previously published in any language, including the abstract and whether the paper is currently under consideration elsewhere for publication.

Title page: Include on the title page (a) complete manuscript title; (b) authors' full names, in order from first to last authors; state first name (given name) then last name (family name), highest academic degrees, and affiliations; (c) name and address for correspondence, including fax number, telephone number, and email address; (d) address for reprints if different from that of corresponding author; (e) all sources of support, including pharmaceutical and industry support, that require acknowledgment; (f) the URL (website address) and trial identification number; (g) disclosure of funding received for this work from any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); and other(s); and (h) the word count of the manuscript body (excluding abstract except in Case Reports, keywords, references and figure legends), number of figures and number of tables.

All relevant conflicts of interest and sources of funding must also be included on the title page of the manuscript with the heading "Conflicts of Interest and Source of Funding." If there is no conflict of interest, this should also be explicitly stated as none declared.

On a separate page, list each author and his/her respective roles in the submitted work, documenting appropriate input for authorship (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html#two).

Title length: The manuscript title should have no more than 120 characters including spaces. Keywords for referencing should be included in the title. Please no

abbreviations. Fancy or comical titles are inappropriate and will be asked to be revised. Trade names of drugs and other products must not appear in the article title.

Structured abstract and key words: Please refer to the table above for abstract requirements for various article types. Do not cite references in the abstract. Limit the use of abbreviations and acronyms. At first mention, please write out the full term for abbreviations (e.g. Celiac Disease (CD)). Use the following subheads in your structured abstract: Objectives, Methods, Results, and Conclusions.

For Keywords, list three to five key words that are not included in the title.

What is Known/What is New: Immediately following the abstract (in the manuscript WORD file) for all article types except where indicated in chart above, authors should include text for a summary box that will be published on the first page of all accepted articles. This text should highlight the significance of the article with the following guidelines in mind: What is known about this subject? What are the new findings and/or what is the impact on clinical practice? Use the format:

- What is known (2-4 bullet points listed beneath this heading)
- What is new (2-4 bullet points listed beneath this heading)

The total text should not exceed 100 words. As this section should be able to stand alone, at first mention of an abbreviation, please write out the full term.

Text: Organize the manuscript into four main headings: Introduction, Methods, Results, and Discussion. If a brand name is cited, supply the manufacturer's name and address (city and state/country). Under Methods, include ethical approval information, if applicable.

Data Analysis: Description of data analyses should provide the specific methods used, their rationale, their assumptions, whether data met those assumptions, and how any missing data were handled. Try to include confidence intervals rather than or with p-values as appropriate.

Abbreviations: For a list of standard abbreviations, consult the Council of Biology Editors Style Guide (available from the Council of Science Editors, 9650 Rockville Pike, Bethesda, MD 20814) or other standard sources. Write out the full term for each abbreviation at its first use in abstract, what is known, manuscript body and in each table and figure unless it is a standard unit of measure.

References: Please adhere to the reference limits noted for each article type above. The authors are responsible for the accuracy of the references. Key the references (double-spaced) at the end of the manuscript. Cite the references in text in the order of appearance. Cite unpublished data—such as papers submitted but not yet accepted for publication and personal communications, including email communications—in parentheses in the text. If there are more than three authors, name only the first three authors and then use et al. Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names, or access the list at http://www.nlm.nih.gov/tsd/serials/lji.html.

Sample references:
Journal article
I. Rautava S, Lu L, Nanthakumar NN, et al. TGF-β2 induces maturation of immature human intestinal epithelial cells and inhibits inflammatory cytokine responses induced via the NF-κB pathway. J Pediatr Gastroenterol Nutr 2012;54:630-8.

Book chapter
2. Todd VR. Visual information analysis: frame of reference for visual perception. In: Kramer P, Hinojosa J, eds. Frames of Reference for Pediatric Occupational Therapy. Philadelphia: Lippincott Williams & Wilkins; 1999:205–56.

Entire Book
3. Ming S-C, Goldman H. Pathology of the Gastrointestinal Tract. Philadelphia: Lippincott Williams & Wilkins; 1998.

Software
4. Epi Info [computer program]. Version 6. Atlanta: Centers for Disease Control and Prevention; 1994.

Online journals
5. Friedman SA. Preeclampsia: a review of the role of prostaglandins. Obstet Gynecol [serial online] January 1988;71: 22-37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

Database
6. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996.

World Wide Web
7. Sullivan D. Major search engines and directories. SearchEngineWatch Web site. http://www.searchenginewatch.com/links/article.php/2156221. Published May 8, 2011. Accessed July 13, 2012.

Figure legends: Each figure must have a legend. Legends should be brief (no more than 100 words) and should be typed on a separate manuscript page, directly following the reference list. Use scale markers in the image for electron micrographs, and indicate the type of stain used. Please let the editors and reviewers know if any of the figures (e.g., figures of study design) are appropriate for the on-line supplemental digital content (SDC) rather than needing to be in-print version.

Figures:
A) Creating Digital Artwork

- Learn about the publication requirements for Digital Artwork: http://links.lww.com/ES/A42
- Create, Scan and Save your artwork and compare your final figure to the Digital Artwork Guideline Checklist (below).
- Upload each figure to Editorial Manager in conjunction with your manuscript text and tables.

B) Digital Artwork Guideline Checklist

- Artwork should be saved in TIFF, Word Doc, PPT or EPS format (PDF is not recommended).
- Artwork is created as the actual size (or slightly larger) it will appear in the journal. (To get an idea of the size images should be when they print, study a copy of the journal to which you wish to submit. Measure the artwork typically shown and scale your image to match.)
- Crop out any white or black space surrounding the image.
- Diagrams, drawings, graphs, and other line art must be vector or saved at a resolution of at least 1200 dpi.
- Photographs, radiographs and other halftone images must be saved at a resolution of at least 300 dpi.
- Photographs and radiographs with text must be saved as postscript or at a resolution of at least 600 dpi.
- Each figure must be saved and submitted as a separate file. Figures should not be embedded in the manuscript text file.

C) Remember:

- Cite figures consecutively in your manuscript.
- Number figures in the figure legend in the order in which they are discussed.
- Upload figures consecutively to the Editorial Manager web site and number figures consecutively in the Description box during upload.

Tables: Cite tables consecutively in the text and number them in that order. Each table should be submitted as a separate Word document in text format. Each table must have a title. Use footnotes to define abbreviations and for other explanatory detail in a legend below the Tables. Tables should be self-explanatory and must supplement, rather than duplicate, the material in the text. Please let the editors and reviewers know if any of the tables (e.g., large data tables, large demographic tables, etc.) are appropriate for the on-line supplemental digital content (SDC) rather than needing to be in-print version.

Supplemental Digital Content (SDC): Authors may submit supplemental digital content with a submission to enhance their article's text or include text, tables, and figures outside of the specified limits. All supplemental digital content is posted online only. One advantage of including material as SDC is that SDC has no limitation of space or length. SDC may include the following types of content: text documents including very detailed methods, graphs, tables, figures, graphics, illustrations, audio, and video. Authors are encourages to submit related but not essential tables (e.g., large tables of articles cited in a meta-analysis, or a large demographic table of a study population) as SDC.

Notes: All online-only materials will be subject to peer review and published at the Editor-in-Chief's discretion. SDC text will not be copyedited. Submit contente exactly as intended to be displayed (including legends). No errata will be written for SDC content. No patient-identifying information should be used in SDC unless written consent from the patient, the patient's parents or the patient's guardian has been obtained. Documentation regarding this consent must be submitted with the manuscript. Copyright and Permission forms for article content including SDC must be provided at the time of submission.

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- Citations should include the type of material submitted, be clearly labeled as "Supplemental Digital Content," include a sequential number, and provide a brief description of the supplementary content.
    - Example of a citation within text: (See Video, Supplemental Digital Content 1, which demonstrates the degrees of flexibility in the elbow)
- Provide a separate legend of online supplementary materials at the end of the text**.** List each item in the order in which the material is cited in the text. The legends must be numbered to match the citations from the text.

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   For studies falling into the categories covered by these checklists, authors need

to submit a formal checklist at the end of the manuscript at the time of submission. This ensures faster review turnaround since many of the points on the checklist ensure improved ease of review.

10. Ethics: Make sure to include the necessary ethical approval/clearance, clinical trial and/or parental or guardian approval information where applicable. If the submission is a clinical trial, include documentation that the project was registered in a public trials registry prior to enrollment of the first subject.
11. Permissions: If using previously published materials, include permission to re-use the material obtained from the copyright holder as Supplemental Data and acknowledge the source in your legend.
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14. Copyright Transfer Agreement: All co-authors must respond to the e-mail regarding authorship and answer the questionnaire. If they are unable to respond to the e-mail, they must include a completed and signed copyright transfer agreement Submissions cannot be published without them.

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