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# CC –BY Advances in gastrointestinal endoscopy: Shaping diagnosis and therapy of gastrointestinal disorders in children

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**Abstract:** In parallel to the growth of paediatric gastroenterology sub-speciality, gastrointestinal disorders requiring endoscopy for diagnosis or therapy 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.

Generally, endoscopy has shown

superiority in terms of diagnostic yield over earlier methods of diagnosing common as well as rare gastrointestinal disorders.

This review sought to review the recent advances in gastrointestinal endoscopy modalities which have led to the explosion in its use for diagnosis and therapy of different gastrointestinal disorders in children.

## Introduction

Gastrointestinal endoscopy in children and adolescent has evolved over the past 40 years with increasing diagnostic as well as therapeutic indications.<sup>1</sup> Technological advancements in endoscopy design and its devices have contributed to the evolution of paediatric gastrointestinal endoscopy.<sup>2,3</sup> Improvement in sedation and anaesthesia,<sup>4</sup> as well as skills in monitoring of vital signs of patients,<sup>5</sup> during endoscopic procedures have equally added to the explosion of the endoscopic modality of treatment.

Currently children of all age groups including neonates can now be examined endoscopically<sup>6</sup> with high safety records 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,<sup>7</sup> severe gastro-oesophageal reflux disease,<sup>8</sup> eosinophilic oesophagitis, and the inflammatory bowel diseases among others.<sup>6</sup>

Diagnostic and therapeutic varieties of gastrointestinal endoscopy are diverse and include oesophagogastroduodenoscopy, 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.<sup>9</sup>

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,<sup>10</sup> in order to ensure effectiveness.

Medical gastrointestinal endoscopy in paediatric popula-

tion ranging from neonates to adolescents is usually undertaken in most reference centres by certified paediatric gastroenterologists who have been trained in accredited fellowship programmes.<sup>2,9,10</sup> They ensure that standard protocols for effective gastrointestinal endoscopy are maintained including pre-procedure preparation of patients, peri-procedure maintenance as well as continued post-operative care.

## *Indications and Modalities of Paediatric Gastrointestinal Endoscopy*

In parallel to the growth of paediatric gastroenterology sub-speciality, gastroenterological disorders requiring endoscopy for diagnosis or therapy 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. Changing indications for paediatric endoscopy over the past two to three decades have generally influenced the detection and characterization rate of some gastrointestinal disorders,<sup>11</sup> including Coeliac disease,<sup>12</sup> and inflammatory bowel disease, among others.<sup>6,13</sup>

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.<sup>9</sup>

Various expert groups including North American Society for Paediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) and European Society for Paediat

Paediatric gastroenterology Hepatology and Nutrition (ESPGHAN) have assessed the different guidelines for the use of gastrointestinal endoscopy in children.<sup>14</sup> 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 encopresis.<sup>15</sup> 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.<sup>6</sup>

Gastrointestinal symptoms including haematemesis, chronic abdominal pain, persistent vomiting, anaemia, dysphagia, and foreign body ingestion are indications for endoscopy.

Oesophagogastroduodenoscopy (upper gastrointestinal endoscopy) is particularly useful endoscopic modality 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.<sup>6,16</sup>

Colonoscopy (lower gastrointestinal endoscopy) is another endoscopic modality which 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 cause of allergic colitis, colitis caused by other conditions like granulomatous diseases including mycobacterium organisms as well as lower gastrointestinal haemorrhage, chronic diarrhoea, cancer surveillance 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.<sup>17,18</sup>

With further technological advancements newer modalities of endoscopy have been developed including small bowel enteroscopy (double balloon enteroscopy), narrow band imaging, endoscopic retrograde cholangiopancreatography (ERCP), wireless capsule endoscopy with higher diagnostic and therapeutic potentials.<sup>6</sup>

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.<sup>3,19</sup>

#### *Consent issues:*

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 or her primary caregivers.<sup>9</sup> Early emotional and psychosocial support of the child as well as the patients/caregivers is beneficial for the endoscopic procedures particularly in centres where conscious sedation is used.<sup>20</sup> The parents/legal guardian of the child should be adequately counselled about the procedure as well as 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.

Informed consent should ideally 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.<sup>9</sup> At the point of consent, the nature of the procedure including risk of anaesthesia and its possible complications should be explained.

#### *Pre-procedure assessments*

Here a complete physical examination is ascertained. Emphasis is also laid on the respiratory and cardiovascular system. Also it is important to exclude possibilities of the child having loose tooth/teeth and enlarged tonsils as they could compromise the airway in sedated patients.

Generally all patients to be anaesthetized should have a thorough pre-procedure anaesthetic review and should be certified fit prior to the procedure.

Basic laboratory tests including a full blood count should be documented. In cases of possible endoscopic therapeutic interventions like variceal banding, sclerotherapy it is important that platelet count, coagulation profile and liver function tests are determined prior to the procedure and adequate interventions put in place including provision of relevant blood product at the point of the procedure. Endoscopy should be deferred in patients with severe coagulopathy as it should be corrected accordingly.<sup>6</sup>

#### *Patient Preparations*

General anaesthesia is known to decrease the protective laryngeal reflexes and to increase the risk of pulmonary aspiration. The American Society of Anaesthesiologists (1999), Association of Paediatric Anaesthetists of Great Britain and Ireland (2003), and European Society of Anaesthesia (2005), the times needed are 2 hours of pre-operative fasting for clear fluids, 4 hours of fasting for breast milk, and 6 hours of fasting for solids.<sup>21</sup> Further as part of the pre-colonoscopy preparations adequate bowel cleansing of the patient with standard bowel preparation regimens prior to the endoscopic procedure

is essential for a clear endoscopic field.<sup>22</sup> Various cleansing regimens including polyethylene glycol with electrolytes, polyethylene with normal saline enema, bisacodyl suppositories are in use either singly or in combination.<sup>23</sup> 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 centre.<sup>3</sup> This bowel preparation should be emphasized so as to allow for a clear visible gut during the colonoscopies. Some gastrointestinal endoscopic procedures require pre-procedural parenteral antibiotic prophylaxis such as during percutaneous endoscopic gastrostomy (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,<sup>24</sup> and as well as local experience.

#### *Intra – Procedure Monitoring*

Patient 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.<sup>25</sup> 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 often without showing obvious signs and symptoms.<sup>3</sup>

#### *Diagnostic yields*

The sensitivity 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,<sup>26</sup> reported an 85% ability of the oesophagogastroduodenoscopy to pick up source of upper GI bleeding in a cohort of 23 patients. In another study of 16 patients undergoing upper gastrointestinal endoscopy in six out of the 16 patients (37.5%), had endoscopically detected abnormalities despite normal radiographic reports.<sup>27</sup>

The results of biopsy in endoscopic procedures have markedly improved the diagnosis of some gastrointestinal diseases including *Helicobacter pylori* infection related gastric and small intestinal ulcers, Coeliac disease, inflammatory bowel disease and associated secondary infections during acute flare up of ulcerative colitis including Cytomegalovirus colitis/infection.<sup>28</sup>

Biopsy tissues taken during colonoscopic procedures from abnormal and even macroscopically normal parts of the gut has 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 la-

belled as possible cases of Inflammatory Bowel Disease particularly Crohn's disease and its treatment with various immunosuppressive therapy and the attendant side effects as well as indirect economic costs to the child and affected families.<sup>29</sup>

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 diagnosis 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<sup>30</sup> the overall rate of change of management after endoscopic evaluation in children with Inflammatory Bowel Disease was 42% necessitating addition of a new medication as the most common intervention.

#### *Complications*

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.<sup>20,24,31,32</sup> In a cross-sectional database review of the complications arising from oesophagogastroduodenoscopy (EGD) 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 EGD. The most common complications noted in that study were hypoxia (1.5%) and bleeding (0.3%). Higher complication rate was more in the youngest age group who desaturates easily, those with highest American Society of Anesthesiologists (ASA) class, and those who received intravenous sedation rather than general anaesthesia.<sup>24</sup>

Absolute contraindication for gastrointestinal endoscopy 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 thrombocytopenia, 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.<sup>3,33,34</sup>

#### *Paediatric gastrointestinal endoscopy in sub-Saharan Africa*

Huge gap exists on gastrointestinal endoscopy practice in children in sub-Saharan Africa with limited data reported jointly by adult physicians and paediatricians in Zambia,<sup>35</sup> Sudan,<sup>36</sup> Egypt,<sup>37</sup> and Nigeria.<sup>38-41</sup> Currently comprehensive paediatric endoscopy training and service in the sub-Saharan African region exists only in the Republic of South Africa where certified sub-specialty training in gastroenterology is obtainable.

Many paediatricians from different sub-Saharan African countries are now being trained as sub-specialists in

gastroenterology from South African institutions<sup>42</sup> and will form the critical mass that will drive rapid expansion in the paediatric gastrointestinal endoscopy services in the region to meet the increasing need.

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## Conclusion

Gastrointestinal endoscopy in children and adolescent has evolved over the past few decades with increasing diagnostic and therapeutic indications owing to new technological advancements in endoscopy design and its

devices.

These changing indications for paediatric endoscopy over the past two to three decades have generally influenced the detection, characterization rate and therapy of diverse gastrointestinal disorders with promising results. Efforts are being made to establish and improve gastrointestinal endoscopy services and training to match the rising demand for paediatric endoscopy in the sub-Saharan African region.

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## References

1. Trigali A, Thomson N, Dumonceau JM, Tavares M, Tabbers MM, Furlano R, et al. Pediatric gastrointestinal endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) and European Society for Paediatric Gastroenterology Hepatology and Nutrition Guideline - Executive Summary. Published online: 2016 Endoscopy. Georg Thieme Verlag KG Stuttgart, New York. DOI: <http://dx.doi.org/10.1055/s-0042-111002>.
2. Nel ED. A brief review of the history of paediatric gastroenterology. *South Africa Gastroenterology Review* 2013; 11:16-18.
3. Belsha D, Bremner R, Thomson M. Indications for gastrointestinal endoscopy in childhood. *Arch Dis Child* 2016; 0:1-8. DOI:10.1136/archdischild-2014-306043.
4. Lightdale JR. Sedation for Paediatric endoscopy. Technique in Gastrointestinal Endoscopy 2013; 15:3-8 DOI: <http://dx.doi.org/10.1016/j.tgie.2012.10.001>.
5. Vargo JJ, Zuccoro G. Jr, Dumot JA, Cornell DL, Morrow JB, Shay SS. Automated graphic assessment of respiratory activity is superior to pulse oximetry and usual assessment for the detection of early respiration depression during therapeutic upper endoscopy. *Gastrointestinal Endoscopy* 2002;55:826-831.
6. Friedt M, Welsch S. An update on paediatric endoscopy. *European Journal of Medical Research* 2013; 18-24. Available from: <http://www.eurjmedres.com/content/18/1/24>. Accessed:18<sup>th</sup> October, 2016.
7. Rubio – Tapai A, Hill ID, Kelly CP, Calderwood AH, Murray JA. ACG Clinical guidelines: Diagnosis and management of Celiac disease. *American J Gastroenterology* 2013; 108: 656-676. Doi:10.1038/ajg.2013.79.
8. Vandenphes Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPHAGAN) and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr* 2009; 49: 498-547.
9. NASPGHAN Guideline: Modifications in endoscopic practice for pediatric patients. *Gastrointestinal Endoscopy* 2014; 79: 699-710. DOI: <http://dx.doi.org/10.1016/j.gie.2013.08.014>.
10. Leichetner AM, Gillis LA, Gupta S, Heubi J, kay M, Narkewicz MR, Rider EA, et al. NASPGHAN Guidelines for training in pediatric gastroenterology. *J Pediatr Gastroenterol Nutr* 2013;56 (Suppl I): S1-38.
11. Franciosi JP, Fiorino K, Ruchelli E, Shults J, Spergel J, Liacouras CA, Leonard M. Changing indications for endoscopy in children over a 20 year period. *J Pediatr Gastroenterol Nutr* 2010; 51: 443-447.
12. Communication from the American Society for Gastrointestinal Endoscopy. The role of endoscopy in the management of GERD. *Gastrointestinal Endoscopy* 2015;81:1305-1310. Doi: 10.1016/j.gie.2015.02.021.
13. Khan MR, Ahmed S, Ali RS, Maheshwari PK. Spectrum of upper GI endoscopy in pediatric population at a tertiary care centre in Pakistan. *Open J Pediatrics* 2014;4:180-184.
14. Guariso G, Meneghel A, Pozza LVD, Romano C, Dalla'Oglio L, Lombardi G, et al. Indications for gastrointestinal endoscopy in children with dyspepsia. *J. Pediatr Gastroenterol-Nutr* 2010; 50:493-499.
15. American Standards of Practice Committee, Lightdale JR, Acosta R, Shergill AK, Chandrasekhara V, Chathadi K, Early D, et al. Modifications in endoscopic practice for pediatric patients. *Gastrointest Endosc* 2014;79:699-710. DOI: 10.1016/j.gie.2013.08.014.

16. Grimaldi- Bensouda L, Abenhaim L, Michaud L, Mouterde O, Jonville- Bera AP, Giraudreau B, et al. Clinical features and risk factors for upper gastrointestinal bleeding in children: a case controlled study. *Eur J Clin Pharmacol* 2010;66:8831-837.
17. Park JH. Role of colonoscopy in the diagnosis and treatment of pediatric lower gastrointestinal disorders. *Korean J. Pediatr* 2010; 53:824-829.
18. Thomson M. Colonoscopy and enteroscopy. *Gastrointest Endosc Clin N Am* 2001;11:603-639.
19. Gralnek IM, Cohen SA, Ephrath H, Napier A, Gobin T, Sherrod O, et al. Small bowel capsule endoscopy impacts diagnosis and management of pediatric inflammatory bowel disease: a prospective study. *Digestive Diseases Science* 201;257:465-471.
20. Mahajan L, Wyllie R, Steffen R, Kay M, Kitaoka G, Dettore J, et al. The effects of a psychological preparation program on anxiety in children and adolescents undergoing gastrointestinal endoscopy. *J Pediatr Gastroenterol Nutr* 1998;27: 161-165.
21. Smith I, Kranke P, Murat I, et al. Perioperative fasting in adults and children: Guidelines from the European Society of Anaesthesiology. *J Anaesthesiology* 2011;28:556-569.
22. Hunter A, Mamula P. Bowel preparation for pediatric colonoscopy procedures. *J Pediatr Gastroenterol Nutr* 2010; 51:524-561.
23. Dehghani SM, Javaherizadeh H, Haghighat M, Imanieh MH, Ghanbari S. Bowel preparation before coloscopy for children: comparison of efficacy of three different methods. *Arq Gastroenterol* 2015;52:311-328.
24. Kay M, Wyllie R. Esophagogastroduodenoscopy and related techniques in: Wyllie R Hyams JS, Kay M (eds) Pediatric gastrointestinal and liver disease, 4<sup>th</sup> edition, Elsevier Saunders, Philadelphia 2011:629-649.
25. Cote CT, Wilson S. Guidelines for monitoring and management of paediatric patients and after sedation for diagnostic and therapeutic procedures: an update. *Pediatrics* 2006;118:2587-2602.
26. Chang MT, Wang TH, Hsu JY, Lee TC, Wang CY, Yu JY. Endoscopic examination of the upper gastro-intestine. *Endosc* 1983;29 5-17.
27. Suzuki H, Kato J, Kuriyama M, Hiraoka S, Kuwaki K, Yamamoto K. Specific endoscopic features of ulcerative colitis complicated by cytomegalovirus infection colitis *World J Gastroenterol* 2010; 16:1245-1251.
28. Wyllie R, Kay MLT. Gastrointestinal endoscopy in infants and children. *Pediatrics in Review* 1993; 14: 351-559.
29. Rathi P, Gambhire P. Abdominal tuberculosis. *J Association of Physicians of India* 2016; 64:38-47.
30. Thakkar K, Lucia CJ, Ferry GD, McDuffie A, Watson KL. Repeat endoscopy affects patient management in paediatric inflammatory bowel disease. *American J Gastroenterology* 2009; 104: 722-727.
31. Hsu EK, Chugh P, Kronman MP, Markowitz JE. Incidence of perforation in paediatric GI endoscopy and colonoscopy: an 11 year experience. *Gastrointestinal Endoscopy* 2013; 77: 960-966.
32. Balsells F, Wyllie R, Kay M, Steffen R. Use of conscious sedation for lower and upper gastrointestinal endoscopic examinations in children, adolescents and young adults: a 12 year review. *GastrointestEndosc* 1997; 45: 375-380.
33. Thakker K, El-Serag HB, Mattek N, Gilger M. Complications of pediatric colonoscopy: a five year multicentre experience. *Clinical Gastroenterology and Hepatology* 2008; 6: 515-520.
34. Gilger MA, Cold BD. Pediatric endoscopy: new information from the PEDS –cori project. *Gastroenterol Rep* 2005; 7:234-239.
35. Mudawi HM, El Tahir MA, Suleiman SH, Eltaybe NH, Gamer NM, Abdalla FA, Ibrahim SZ. Paediatric gastrointestinal endoscopy. *Eastern Mediterranean Health* 2009;15:1027-1031.
36. Kelly P, Katema M, Amadi B, Zimba L, Aparico S, Mudenda V, Baboo KS, Zulu I. Gastrointestinal pathology in University Teaching Hospital, Lusaka, Zambia: review of endoscopic and pathology records. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2008;102:194-199.
37. Abu Faddan NH, Eltyeb A, Baraakat M, Gamal Y. Gastrointestinal endoscopic practice in infants: indications and outcome. *Egyptian Pediatric Association Gazette* 2016;64:160-166.
38. Ikobah JM, Ngim OE, Adeniyi F, Ekanem EE, Abiodun P. Paediatric endoscopy in Nigeria humble beginning. *Niger J Paed.* 2015;42:147-150.
39. Alatise OI, AnyaboluHC, Sowande O, Akinola D. Paediatric endoscopy by adult gastroenterologists in Ile- Ife, Nigeria: A viable option to increase the access to paediatric endoscopy in low resource countries. *African J Paediatric Surgery* 2015;12:261-265.
40. Adeniyi OF, Lesi OA, Odeghe EA, Adekola O, Oduwole A. Upper gastrointestinal endoscopy in children: The Lagos University Teaching Hospital experience. *S Afr J. Child Health* 2016;10: 207.
41. Ray- Offor E, Elenwo SN. Endoscopic evaluation of upper and lower gastro-intestinal bleeding. *Niger J. Surg* 2015;21:106-110.
42. Swinger G, Hendricks M, Hall D, Hall S, Sanders D, McKerrow N, et al. Can a new paediatric sub- specialty improve child health in South Africa? *South Afr Med. J.* 2012;102:738-739.