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Indocyanine Green Angiography in Pediatric Colorectal Surgery

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Surgery

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Abstract

Hirschsprung Disease (HD) and Anorectal Malformations (ARM) are congenital colorectal conditions that necessitate surgical correction via bowel resection with the creation of an anastomosis. Surgical complications, thought to be in part due to malperfusion of the bowel anastomosis, are frequent, as revealed by the retrospective review enclosed. Indocyanine Green Angiography (ICGA) is a process in which water-soluble dye (ICG) is used to assess perfusion of tissue, and it has been employed with success in adult populations to reduce rates of anastomotic leak during colorectal surgery. The systematic review conducted within confirms that this tool has not been extensively studied in pediatric patients undergoing bowel resection. To understand the feasibility of conducting an adequately powered multi-centered trial to determine if ICGA reduces the rates of malperfusion-related complications such as anastomotic stricture, leak, or dehiscence during pull-through for HD or ARM, a feasibility randomized controlled trial was conducted. We found that the designed protocol achieved a recruitment rate of 80%, which met our prespecified criteria to proceed with a larger study. Further research into the utility of ICGA in pediatric colorectal surgery is required.

Keywords

Hirschsprung Disease, Anorectal Malformation, congenital aganglionosis, colorectal surgery, pediatric, indocyanine green, ICG, angiography, anastomotic leak, stricture, dehiscence.

Summary for Lay Audience

Hirschsprung Disease (HD) and Anorectal Malformations (ARM) are conditions that affect the large bowel or colon in around one in 5,000 babies born around the world. HD is caused by nerves in the colon not developing, specifically ganglion cells. This results in the colon not being able to move stool through it properly. Due to this, babies born with HD have symptoms of a bowel blockage. ARM is a term used to describe a spectrum of abnormalities in the development of the rectum and anus. It can range from absence of an anus to an abnormal connection between the rectum and a surrounding structure such as the vagina or bladder.

Both HD and ARM need a surgery to fix them. In HD, the part of the bowel that doesn't have ganglion cells is removed and healthy colon is brought down to the anus. Similarly in ARM, healthy colon is brought through to the skin to form an anus, making sure to fix any abnormal connection, while preserving the muscles in the pelvis that allow children to control their bowel movements. Unfortunately, all surgeries come with risks of complications. It is thought that these complications may be due to the connection (anastomosis) between the colon and anus not having enough blood flow. Some of the complications that occur after repair of HD and ARM include anastomotic strictures (narrowing of the connection), anastomotic leaks (a disruption in the connection, resulting in spillage of stool), and anastomotic dehiscence (the connection between the skin and colon coming apart).

One way to assess the anastomosis for good blood supply is using indocyanine green angiography (ICGA). This is a contrast dye that binds to blood proteins and glows green when a special light is used and there is good blood flow to the area of interest. This technology has been studied in adults with some success but has not been studied in children. We looked at the existing literature and conducted a study to see if a trial designed to find out if ICGA reduces the risks of complications.

Co-Authorship Statement

The co-authors below made significant contributions to this thesis.

Dr. Andreana Bütter and Dr. Kelly Vogt as my supervisors, assisting with study inception and design, as well as editing the manuscript

Dr. Natasha Seemann for contributions to manuscript revisions

Jacob Davidson for assistance in study design, REB and Health Canada Applications, as well as patient identification and recruitment

Dr. Evelyn Waugh for assistance in data analysis for the retrospective review component

Dr. Brendan Santyr as second reviewer for the systematic review component

Darren Hamilton as the medical librarian on the systematic review component

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Chapter 1

1 Introduction

Congenital disorders of the rectum and/or colon have a profound impact on a child and the families who care for them. The most common congenital disorders of the colon and rectum are Hirschsprung disease and anorectal malformations, both of which require surgical intervention. For a variety of reasons, there are substantial risks involved with these procedures. Paediatric surgeons strive to reduce postoperative complication rates to improve quality of life and reduce morbidity and mortality. This thesis focuses on how the perioperative course may be improved for patients with Hirschsprung disease and anorectal malformations, by improving vascular supply to anastomoses during surgical correction.

1.1 Hirschsprung Disease

1.1.1 General Description and Historical Context

Hirschsprung disease (HD), also known as congenital aganglionic megacolon, is a gut motility disorder. It is a result of a failure of neural crest cell migration during fetal development¹. Ganglion cells are essential for colonic motility, and their absence within the bowel wall can result in dysfunctional stooling or acute functional obstruction. The disease was named after a Danish physician named Harald Hirschsprung, although it was first described in the literature by an anatomist named Frederick Ruysch¹. In 1887, Dr. Hirschsprung described two cases, although the pathologic portion was initially thought to be the dilated colon². Swenson described the first successful reconstructive surgery in 1947³. Guided by studies in colonic peristalsis, Swenson's experimental proctosigmoidectomy proved to be curative for an HD patient and the pathogenesis of the disease began to be understood. Since this time, operative techniques have been honed to reduce the rates of post-operative complications, although significant risks remain.

1.1.2 Epidemiology

The incidence of HD is approximately 1 in every 5000 live births in North America and northwestern Europe⁴. The male to female ratio for HD is approximately 4:1 for short segment disease, however it becomes closer to equal between the sexes with longer aganglionic segments⁵. There is strong evidence for a genetic component to the disease, with a 28% chance risk of transmission to a male child of a mother with long segment disease⁵. Additionally, the risk of HD in a sibling ranges from 3% in short segment disease and up to 28% in long-segment disease⁵.

1.1.3 Embryology

Neural crest cells migrate in a craniocaudal direction, and therefore the absence of ganglion cells begins at the distal rectum and extends proximally through the colon to varying degrees. There are differing lengths of colonic involvement, from short segment disease to total colonic aganglionosis to almost complete intestinal aganglionosis. The formation of the ganglion plexus by the joining of neurons and glia in the primitive gut is the basis of the development of smooth muscles along the colon⁶. Absence of these cells and plexi leads to defective development of the enteric nervous system, significantly affecting gut motility.

1.1.4 Pathophysiology

Hirschsprung disease is often described as a disorder of functional obstruction, rather than mechanical obstruction. While the lumen of the colon is technically patent, the stool remains stagnant due to the dysfunction of the enteric nervous system, which results in build-up of stool proximally. This, in turn, can lead to not only dysfunctional stooling, but Hirschsprung-related enterocolitis due to inflammation and bacterial overgrowth, bacterial translocation leading to sepsis or even perforation. It is estimated that 75% of HD patients have disease limited to the rectosigmoid colon, which is considered short segment disease⁷. Long segment disease is considered aganglionosis that extends to the proximal descending colon or splenic flexure and comprises another 15-20% of cases⁸. Total colonic aganglionosis is present in approximately 8% of cases⁸ and can extend into

the small bowel. Total or near total intestinal aganglionosis is rare. Severity of disease usually correlates with the length of affected bowel.

1.1.5 Genetics

There are several gene mutations that have been implicated in the development of HD, the most significant being the RET proto-oncogene^{9,10}. Mutations in the GDNF protein, a ligand of RET, also contributes significantly¹⁰. Researchers have come to understand that HD can be heritable, with 10-20% of cases occurring in individuals with a positive family history¹. HD is associated with genetic syndromes in 30% of patients, with 18% having congenital anomalies¹¹ and chromosomal anomalies in 12% with Trisomy 21 specifically in 7.3% of cases¹². Multiple Endocrine Neoplasia type 2 (MEN2) is characterized by development of neoplasms in neural crest cell derivatives and is present at a greater than population average in patients with long segment disease and total colonic aganglionosis¹³. This is specifically thought to be due to a mutation in the RET proto-oncogene, which can be the causative agent of both conditions. Several other syndromes are also associated with the condition, including central hypoventilation syndrome, neurocristopathy syndromes (specifically Waarenburg syndrome type 4A), Mowat-Wilson syndrome, Goldberg-Shprintzen syndrome, and Smith-Lemli-Opitz syndrome¹⁴. Presence of associated genetic syndromes has been associated with delays in diagnosis, increased risk of Hirschsprung related enterocolitis, and increased rate of post-operative complications, particularly in those with Trisomy 21¹⁵. Leading theories surrounding this observation include associated conditions accounting for failure to thrive (such as congenital heart disease) and intrinsic T lymphocyte activity resulting in a propensity for enterocolitis¹⁵.

1.1.6 Presentation and Diagnosis

The most frequently observed sign of HD is failure to pass meconium within 24 hours after birth, occurring in approximately 90% of patients with HD¹⁶. Other symptoms and signs of obstruction include bilious vomiting, abdominal distension, and obstipation. If unrecognized, the functional obstruction caused by HD may progress to bowel perforation in 5% of patients. Hirschsprung related enterocolitis can also be a presenting

symptom, and should be suspected in an infant with sepsis, abdominal distention, and diarrhea.

Approximately 90% of patients are diagnosed in the first 3 years of life, with patients with a short segment of affected bowel typically presenting later¹⁷. Some efforts have been made to identify signs of HD on prenatal ultrasound, however retrospective reviews demonstrate that most prenatal scans are normal^{18,19}. For patients diagnosed later in childhood, chronic constipation is typically the chief complaint. Due to the distended colon leading to a sensation of fullness, these children are often malnourished. The “squirt sign” is a physical examination finding highly suggestive of HD in which when digital rectal exam is performed, a high pressure of stool and air in the rectum is released²⁰.

Typically, patients undergo non-invasive imaging (i.e., contrast enema) as the first investigation when HD is suspected. A contrast enema that would be suggestive of HD would demonstrate a transition point between dilated and non-dilated bowel, an abnormal rectosigmoid ratio (<1), “sawtooth” contractions in the rectum, and retained contrast past 24 hours in term infants^{21, 22}. Contrast enemas performed in the neonatal period demonstrate an 80% sensitivity for HD, and a 98% specificity²², however these statistics vary depending on the child’s age²³. Inconclusive enema studies present a diagnostic dilemma at times as to when to pursue more invasive investigations. A rectal biopsy is the gold standard for diagnosis of HD with a pathologist examining the submucosal sample for the presence or absence of ganglion cells²¹. The biopsy itself can be done with a suction biopsy device, as a bedside or clinic procedure in the first six months of life. Rectal biopsies aim to sample rectal mucosa and submucosa at least 2 cm or higher from the dentate line since the first 1-2 cm proximal to the dentate line has known physiologic aganglionosis²⁴.

1.1.7 Treatment

1.1.7.1 Historical Context

HD is a disease that requires surgical correction. As this condition affects bowel in a distal to proximal fashion, dissection of the rectum and resection of all diseased bowel is

necessary. The mainstay of treatment is what is referred to as a “pull-through” due the nature of bringing the healthy bowel down to the perineal margin²⁵. This technique was initially developed by Swenson in the 1940s and expanded upon by Soave and Duhamel to better preserve pelvic vascularity and innervation²⁶.

Previously, a colostomy was routinely performed during the initial operative repair. This has largely fallen by the wayside, as evidence grew in the 1980s demonstrating no significant increase in complications with a one stage approach without colostomy^{27,28}. Colostomy is still used, based on the discretion of the surgeon, in cases where patients present with severe enterocolitis, perforation, or total colonic agangliosis²⁶.

The first description of a laparoscopic approach to pull-through surgery was in the 1990s²⁹. The surgeon laparoscopically mobilizes the rectum and colon and obtains colonic biopsies to identify the transition zone and aganglionic segment³⁰. Many centers now perform a laparoscopic-assisted approach, while others prefer a transanal only approach³¹. A purely transanal approach is possible in patients with shorter segment of Hirschsprung disease isolated to the rectum or distal sigmoid colon. However, a more proximal transition zone requires more extensive mobilization and identification of ganglion cells in colon inaccessible through a transanal approach, necessitating an abdominal approach. Those patients with long-segment HD are the ones who stand to benefit the most from a laparoscopic approach allowing a minimally invasive surgical technique. The addition of laparoscopy ensures proper orientation of the bowel and allows for transabdominal dissection of the rectal planes before committing to definitive resection. With the upper portion of the rectum dissected out laparoscopically, this reduces the amount of dissection required trans-anally. This is thought to result in better long-term bowel function due to reducing the amount of time and degree that the anal sphincter muscles are stretched.

1.1.7.2 Laparoscopic-assisted endorectal pull-through³²

A laparoscopic approach enables the abdominal dissection that traditionally would have been completed in an open fashion via laparotomy or a prolonged transanal approach. Compared to a completely transanal approach, the laparoscopic assisted method allows

for more careful mobilization of the colon vascular pedicle¹⁹. The patient still requires dissection of the distal rectum using a transanal approach to complete the surgery.

With the patient in the supine position, insufflation of the abdomen is obtained through a laparoscopic port at the umbilicus. Typically, two additional trocars are inserted, one in the left lower quadrant and one in the right lower quadrant. Biopsies are then taken from areas above and below the transition zone from dilated to non-dilated bowel. These biopsies are sent to pathology for frozen section to ensure the proposed resection margin contains ganglion cells. If there is no clear transition zone, sequential biopsies must be taken every 5-8 cm until ganglion cells are identified. Occasionally, if frozen sections are unable to identify any ganglion cells throughout the colon despite multiple frozen sections, definitive pull-through may need to be deferred until permanent full thickness biopsies can be examined by a pathologist. This is to avoid total colectomy and ileoanal anastomosis in patients without total colonic aganglionosis.

Once the area of healthy bowel containing ganglion cells is identified and marked with a suture, mobilization of the left colon is carried out by dissecting along the white line of Toldt. Dissection is continued distally into the pelvis, which will later be met circumferentially by the dissection performed from the transanal approach. During mobilization, special care is taken to conserve the marginal artery, an important part of collateral circulation for the bowel that will become the anastomotic site. Whether or not the inferior mesenteric artery must be divided depends on the length of aganglionic bowel. To accomplish the proctectomy component of the operation, the superior hemorrhoidal vessels must be taken. This essentially leaves branches of the inferior mesenteric artery (if preserved) and the marginal artery as the remaining blood supply to the colon. The surgeon typically assesses if there is enough length of bowel to reach the dentate line by grasping bowel approximately 20 cm upstream from the proposed anastomosis site and seeing if it can be brought down to the pelvis without tension. Once adequate mobilization is complete, the abdomen is desufflated and trocar sites are closed. The surgeon then proceeds with the transanal dissection. The perineum is prepped and draped, with the patient supine with legs up and splayed. Traction sutures, or alternatively a traction device such as the Lone Star Retraction System© is placed circumferentially

along the anal verge. Starting 1-2 cm above the dentate line, a submucosal flap is created circumferentially, staying close to the rectal wall to avoid injuring pelvic innervation, vasculature, or the sphincter complex. During this process, perforating vascular branches from the middle and inferior rectal arteries must be taken to facilitate mobilization. Eventually the previously dissected sigmoid colon is delivered through the endorectal dissection margins, as is the suture marking the biopsy site demonstrating ganglionic bowel. This portion of bowel is then opened, and a Hagar dilator is placed within it to ensure the bowel has not been twisted. The laparoscope is also used to verify that the ganglionic bowel is straight.

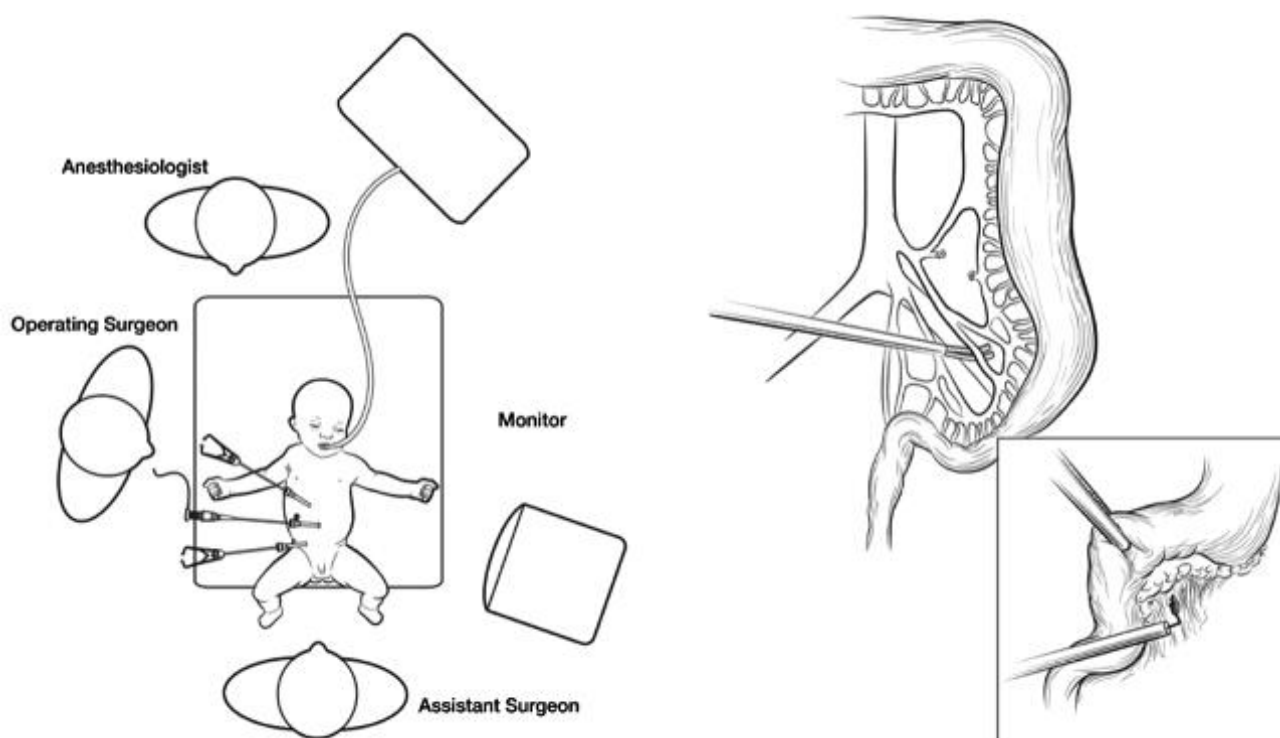


Figure 1: Laparoscopic-assisted pull-through for Hirschsprung Disease. Reprinted from “Laparoscopic and transanal pull-through for Hirschsprung disease” with permissions by J. Langer, 2012, *Seminars in Pediatric Surgery*, 21(4), pages 283-290. Copyright Elsevier²⁶

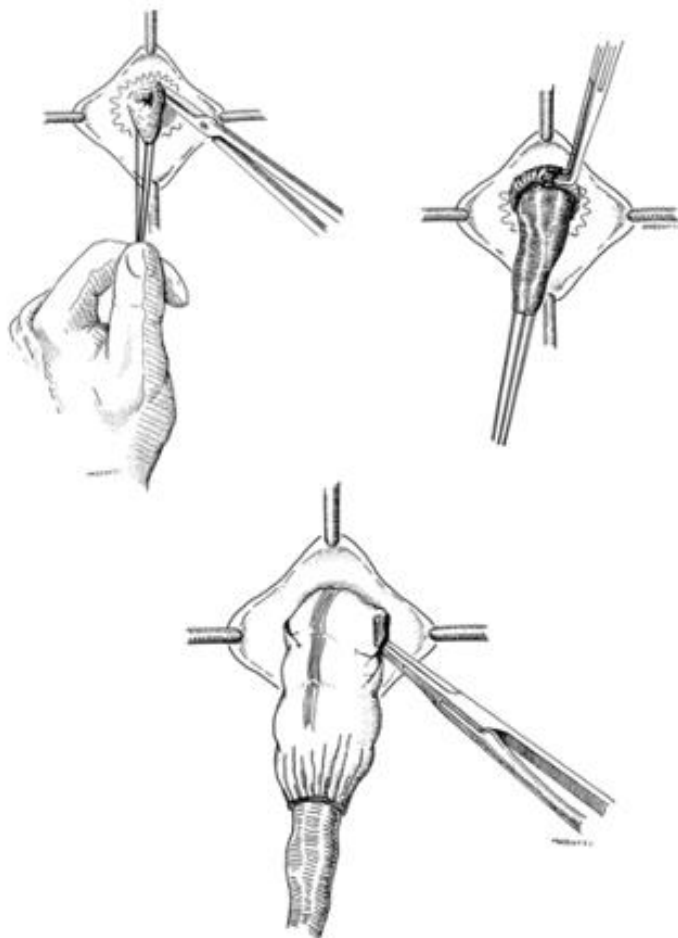


Figure 2: Pull-through procedure for Hirschsprung disease. Reprinted from “Laparoscopic and transanal pull-through for Hirschsprung disease” by J. Langer, 2012, *Seminars in Pediatric Surgery*, 21(4), pages 283-290. Copyright (2012) by Elsevier²⁶

Of particular relevance to this thesis, intraoperative decision making in terms of length of bowel to be resected traditionally depends on a) pathologic visualization of a transition point, b) confirmation of the presence of ganglion cells in the proposed resection margin (via frozen section), and c) viability of the bowel. Depending on the amount of bowel resected and the individual patient’s anatomy, major vascular pedicles may need to be taken, leaving the bowel’s perfusion dependent on a less dependable collateral blood supply. Surgeons use typical means of assessing blood supply prior to anastomosis such

as inspecting for a bleeding edge, colour of the bowel, and observation of peristalsis. There is limited scientific data on the accuracy of these modalities, largely limited by the lack of alternative means. A study from 1981 suggested that the accuracy of conventional means compared to myoelectric and color analysis is in the realm of 89% in the case of small bowel ischemia, however this was compared to a method including outdated fluorescein technology and doppler, without a second-look operation³³. Conventional visual modalities of assessing bowel viability are an important aspect of assessing viability, however this is certainly subject to inter-rater variability and human error.

Debate is still ongoing with regards to the optimal timing of definitive corrective surgery for Hirschsprung disease. Many surgeons wait until the child is at least a few months of age prior to proceeding with operative management, since they believe there is greater perioperative risk in the neonatal period. However, delaying surgical management has the potential for developing Hirschsprung related enterocolitis (HAEC), with the risk of HAEC being as high as 25% in the preoperative period³⁴. Although this risk can be mitigated by performing daily, or twice daily, serial irrigations of the rectum and colon to promote decompression, one needs to weigh the risks and benefits of early vs late pull-through³⁵. A systematic review conducted in 2021 suggested that patients treated with definitive pull-through at less than 2.5 months of age tended to have worse outcomes, including substantially higher risks of stool soiling, stricture, and leak³⁶. Factors such as geographic location and parental compliance with routine irrigations need to be considered i.e., a child who lives far away from a Children's Hospital should have their pull-through early since if they developed HD enterocolitis, they could die from sepsis prior to timely return to hospital.

1.2 Anorectal Malformation

1.2.1 General Description and Historical Context

Anorectal malformations (ARM), sometimes referred to as imperforate anus, is a variable disease manifesting as abnormalities in the location or presence of the anus and/or rectum. It also occurs in approximately 1 in 5000 live births³⁷. On external examination, this may manifest as an absent anal opening, a smaller anus, or an anus in an abnormal

location. The term imperforate anus is somewhat misleading, as there is a multitude of anatomical variants that are encompassed by ARM that are not as simple as the absence of an anal opening. They may or may not be associated with a fistula, or abnormal connection to a surrounding structure such as the vagina, urethra, or perineum. Typically, clinicians differentiate them as high vs low malformations, with respect to the agenesis being present above or below the levator muscles of the pelvis. ARMs were first described by Aristotle, with the first treatment attributed to Soranus in the second century, involving cutting and dilation of the anal opening³⁸. Further advancements in treatment were made by Bell in the 18th century, with more apparent malformations, including dissection to a blind ending rectum and description of associated fistulae³⁸. A multitude of iterations in operative management ensued with high rates of perioperative mortality and morbidity before the posterior sagittal anorectoplasty was developed by DeVries and Peña in 1982³⁹.

1.3 Embryology

ARMs are due to derangements in the development of the hindgut. Initially during development, the primitive colon, rectum, bladder, and urethra are an endoderm-lined cloaca. A urorectal septum eventually develops, separating the urinary and gastrointestinal structures. A recanalization of the ectoderm/endoderm junction must occur to form a normal anal-rectal complex. Defects in this recanalization has been hypothesized to be the inciting factor of ARMs. Recanalization can occur to varying degrees, hence why there is significant variation in the anatomy of fully formed ARMs. Fistulae develop to nearby structures, whether they be the urethra, prostate, or perineum, based on the degree of recanalization³⁸.

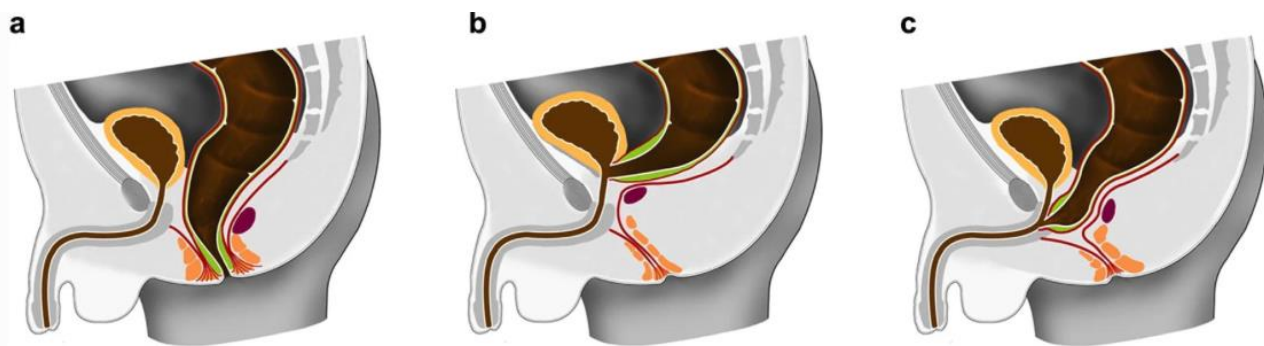


Figure 3: Variations in anorectal malformation anatomy. “a” normal anatomy. “b” fistula to the bladder, “c” rectovaginal fistula. From “Normal anorectal musculatures and changes in anorectal malformation”, Li et al., 2012 with permissions. Copyright Springer⁴⁰

1.3.1 Pathophysiology

The pathophysiology of ARMs depends upon the individual patient’s anatomy. Most ARMs have some sort of associated fistula, resulting in defecation through the associated tract, whether it be the bladder, vagina, or displaced perineal opening. Depending on the length and diameter of the associated opening, patients may have varying degrees of mechanical obstruction. This is occasionally detected on prenatal ultrasound by identifying bowel dilatation in utero. However, most patients are only diagnosed postnatally during careful physical examination. Patients with no associated fistula are completely obstructed, while patients with fistulas accessible externally may be able to defecate effectively, particularly with serial dilations of the tract.

1.3.2 Genetics

The risk of having a second child with ARM is approximately 1%, lending credence to the idea that there is a genetic element⁴¹. A study from 2007 found that 1.7% of patients with ARM had at least one family member with a genitourinary or pelvic anomaly⁴¹. Several gene mutations have been identified in the pathogenesis of ARMs. Wnt, Hox genes, and Sonic hedgehog are among the predominant genes involved⁴². Each of these genes have been implicated in embryogenesis. ARMs are associated with other anomalies

in approximately 50% of cases³⁷. The classic association is the VACTERL spectrum of diseases (presence of at least three of: vertebral abnormalities, anorectal malformation, cardiac, tracheoesophageal fistula, renal and limb anomalies). VACTERL is the most frequent syndrome in patients with ARM, making up 56% of those with other anomalies⁴³. In patients with this association, post-operative quality of life may depend on the additional anomalies of the patient (e.g., severity of cardiac disease). 5.1% of patients with ARM have Down Syndrome, and ARM has also been associated with fragile X syndrome and trisomy 8 mosaicism^{44,45}. Interestingly, in patients with Trisomy 21 and ARM, 95% of these have imperforate anus without fistula, compared to only 5% of all patients with ARM⁴⁶. Fortunately, the malperfusion-related post-operative outcomes in Trisomy 21 patients are similar to those without a chromosomal abnormality⁴⁷.

1.3.3 Diagnosis

The mainstay of postnatal diagnosis of ARM is physical examination. Patients may have an abnormal location of anal opening, absent anal opening, or visualizable fistula. If there is a fistula to the urethra, there may be fecaluria. Abdominal radiography may serve as a useful adjunct in assessing for bowel dilatation. It is also necessary to assess neonates with ARM for additional associated anomalies such as cardiac, vertebral, and renal diseases⁴⁸.

1.3.4 Treatment

Treatment of ARM and its timing depends on the individual patient's anatomy and presence of associated anomalies. Male patients with a high fistula to the urethra exhibit more obstructive symptoms and often need a diverting colostomy soon after birth. Conversely, patients with a fistula to the perineum or vagina tend to be able to defecate adequately and can avoid ostomy if they undergo serial fistula dilation to promote decompression. Definitive repair of the ARM is typically done in the first 1 to 3 months of life to avoid formation of a very dilated rectum⁴⁹.

Repair of ARM is typically done via a posterior sagittal anorectoplasty, or PSARP. The technique was first used in 1980 and has become the mainstay of treatment^{50,51}. The

complexity of this repair depends on the individual patient's anatomy. Patients with a cloaca, or a convergence of the urethra, vagina, and anal opening, require creation of an additional wall of tissue essentially, which can be quite difficult. More modern techniques take special care to conserve the anal sphincter complex to maintain long term control⁵¹.

1.3.5 Posterior Sagittal Anorectoplasty

After the patient is intubated, a Foley catheter is placed to assist in identifying the urethra and bladder during dissection. The patient is then placed in the prone position, and the skin is prepped. Using a nerve stimulator, a skin incision is created in the sagittal orientation in the midline. Most patients have an "anal dimple", a small divet where the anus should be. Nerve stimulation ensures accurate identification of the anal sphincter complex. An incision is made over this point, and dissection performed through the subcutaneous tissues until the parasagittal fibres and muscle complex are identified. The pelvic floor muscles form a funnel shape that in normal anatomy encircle the rectum. The surgeon must dissect through the ischioanal fat to reach the levator muscles which are divided sagittally. From here, the location of the rectum varies depending on the location of fistulization. During the entire dissection, the nerve stimulator is frequently used to ensure that one stays exactly in the midline.

Once the rectum is identified, stay sutures are typically placed on the posterior aspect of the rectum. The rectum is then incised, which will serve as the neo-anal opening in conjunction with the fistula itself. Anteriorly, special care is taken to affix the rectal wall to the backside of the urethra or vagina in order to create a new separation between the two. From a perineal approach, the rectum is dissected circumferentially to allow mobilization of the rectum down to the perineum. The previously created opening in the posterior rectal wall is then brought down to skin level. If the delivered rectum is disproportionately large, surgeons may taper the colon by suturing it. Some surgeons also reinforce the wall between the urethra and the rectum by bringing in some of the surrounding musculature. Once it is evident that there is a tension free repair in the area, the rectal opening is sutured to the skin.

1.4 Postoperative Complications

Repair of HD and ARM are the most common colorectal surgeries performed in the neonatal period. While there are definite differences in the pathophysiology of HD and ARM, there are similarities between the operative approach to their correction. Both procedures require mobilization and/or resection of the rectum. Additionally, both involve creating a colo-anal anastomosis. The mobilized bowel and subsequent anastomosis can be subject to impaired perfusion, resulting in postoperative complications. Interventions aimed at preventing these complications would be beneficial. Most of these children survive well into their adult lives with longstanding correction of the abnormalities. Thus, serious post-operative complications need to be avoided at all costs to ensure optimal quality of life.

One of the most dreaded complications following colorectal surgery is an anastomotic leak, in which the newly sewn together bowel comes apart leaving a defect in the bowel wall and allowing feces to enter the surrounding tissue. Among post-operative HD patients, the rate of anastomotic leak has been estimated to be approximately 7% based on a single-center retrospective review including 82 patients in 1996⁵². This complication comes with high rates of morbidity, including wound infection, sepsis, and shock. Most patients with anastomotic leak require additional surgical procedures, typically on an emergent basis.

Wound dehiscence is a related serious complication of colorectal surgery, usually characterised by drainage, pain, fibrin or mucous at the anastomotic site, and or retraction of rectum. In terms of HD and ARM patients, this may manifest in an identical manner to anastomotic leak, as the site of anastomosis and the external wound edges are both at the anorectal margin. The bowel may retract into the anal canal, and these patients may require reoperation with or without creation of a diverting ostomy to allow the area to heal.

After repair of ARM or HD, anal stricture can also form. The anastomosis between the bowel and the perineal skin can scar, resulting in narrowing of the bowel lumen. This can result in chronic constipation and irregularities in defecation, which can have a

significant impact on the child's quality of life. In extreme situations, patients may require reoperation in the form of a revision anoplasty or stricturoplasty⁵³. Due to the frequency of stricture formation, specifically in cases of ARM, postoperative anal stricture traditionally has been managed pre-emptively. Patients undergo serial dilations of the neo-anal canal, regardless of whether strictures have formed. This practice was taken up routinely in the 1980's^{39,50}, as prior to this, stricture was the most common indication for reoperation (28% of patients)⁵⁴. More recent data, however, has demonstrated that the rates of clinically significant stricture requiring reoperation are not statistically different, regardless of whether the patient has undergone routine serial dilations^{39,50,54}. In addition, serial dilatations can have significant psychological impact on patients and their families, which may sway clinicians away from this practice^{36,55-57}. Similarly, post-operative stricture is a very common complication among post-operative pull-through patients with Hirschsprung disease, with some studies estimating the rates at approximately 22%⁵². Currently, many pediatric surgeons are opting away from routine postoperative serial dilatations, especially for Hirschsprung disease.

Patient factors and events associated with anastomotic leak, dehiscence, and stricture are multifactorial. Both patient factors and operative factors have been implicated. In terms of patient factors, steroid use and malnutrition have been demonstrated to be important considerations in anastomotic healing^{58,59}. Additionally, some evidence exists in adult literature that perioperative non-steroidal anti-inflammatory (NSAID) use may increase the risk of anastomotic leak⁶⁰. Operative factors relevant to HD and ARM patients are perioperative sepsis, transfusion, low anastomosis, tension on the anastomosis, bowel obstruction, and blood supply^{61,62}. All of these are important considerations during operative intervention for these diseases, however some are not modifiable.

One important and potentially modifiable factor relevant to this thesis, associated with failure of an anastomosis or development of stricture, is tissue ischemia at the site of anastomosis^{61,63}. This has been identified as an area for improvement in the surgical approach to reduce perioperative complications. Studies have identified that ischemia is a key factor in the development of stricture, dehiscence, and leak^{64,65}. Classical methods of identifying poor vascular supply to the anastomosis, such as visual inspection, pulse

palpation, and assessment for a bleeding edge, are very subjective. Furthermore, once the segment of bowel has been pulled through the dissected pelvic musculature, it can be particularly difficult to observe peristalsis and other signs of ischemia given space restraints. An objective method is needed to assess the vascular supply to the proposed bowel to be used for anastomosis.

1.5 Indocyanine Green Angiography

One potential method to improve assessment of the blood supply to the coloanal anastomosis is indocyanine green angiography (ICGA). ICGA has been used in adult populations since the mid-1950s⁶⁶. ICG is a fluorescent iodide dye that binds to plasma proteins and is ultimately cleared hepatically⁶⁷. Immediately after intravenous administration, 98% of ICG binds to serum albumin and α - and β -lipoproteins while the remainder remains unbound and is transported into bile almost immediately^{68,69}. The half-life of the compound is approximately 3-4 minutes, with only trace amounts of ICG that can be detected after one hour^{69,70}. The first major adopter of indocyanine green angiography was in ophthalmology, when it was used for imaging the retina. Since then, it has expanded into the fields of neurosurgery in aneurysm procedures, plastic surgery in skin flap perfusion assessment, and hepatobiliary surgery to discern biliary anatomy⁶⁷. ICG absorbs near infrared light, and once excited, it can be observed at a longer emission wavelength, with the assistance of specialised camera equipment⁶⁷. This technology has been developed in a laparoscopic, overhead, and handheld device format to allow for its application in a range of surgeries. Most relevant to this project is its application in adult colorectal surgery. The use of ICGA for visualizing bowel vascular supply was initially described during low anterior resections where – like the pediatric surgical procedures discussed above – perfusion can be tenuous⁷¹⁻⁷³. One retrospective case-control study looking at ICG use during low anterior resection for rectal cancer suggested a reduced anastomotic leak rate when ICG was used, however this study lacked adequate power to make definitive conclusions⁷⁴.

The current evidence for ICGA is, however, mixed. A systematic review and meta-analysis conducted in 2018 amalgamated data from 5 single-center, non-randomized studies, four of which were retrospective, with a total of 1302 patients⁷⁵. This study specifically looked at the potential risk reduction for anastomotic leak and suggested an odds ratio of 0.34 (95% CI 0.16-0.74) when ICG is used in oncologic colorectal surgery. A randomized controlled trial including 252 patients undergoing laparoscopic left colectomy and rectal resection demonstrated that ICG was feasible to perform in routine

operations, but there was no statistically significant difference in anastomotic leak rate⁷⁶. Despite a strong theoretical basis in providing the surgeon a unique opportunity to visualize the vascular supply to the bowel, and some supportive data from observational studies, no large randomized controlled trials have been conducted to evaluate the use of ICGA in colorectal surgery.

The safety of the medication, however, is well established, with an adverse reaction rate of ~0.34%⁷⁷. In a study of 2,820 patients, only 13 had adverse reactions, with most significant being transient hypotension in two individuals requiring vasopressor support⁷⁷. The main contraindication is an allergy to iodine, as anaphylaxis attributed to iodine allergy has been documented to occur at a rate of 0.05%^{78,79}.

1.5.1 ICGA in Pediatric Surgery

While ICGA has been applied in oncologic resections, neurosurgery, and urology within the pediatric surgery realm^{80,81}, it has not been extensively studied in pediatric colorectal surgery. A few small studies and case reports have been performed which have shown that it is safe in pediatric patients^{80,81}. A small study by Rentea *et al.* demonstrated that ICGA can be used during pull-throughs for Hirschsprung Disease and PSARPs for anorectal malformation⁸². The group used ICGA during 13 sequential operations for patients with ARM or HD using a mobile camera head with fluorescence angiography system. The dose of ICG delivered was 0.2 mg/kg, allowing for 3-4 minutes to observe the ICG, the half-life of the agent. Their study did not result in any adverse events attributable to ICG use, and the ICG was visualized in all cases. Surgeons documented the planned resection margin before and after ICG and documented any changes in surgical planning. The use of ICGA was associated with a change of plan in 31% of cases, and the authors concluded that ICG effectively identified impaired vascular supply that have led to post-operative complications, however this was clearly insufficiently powered to detect a difference. Additional information with regards to other applications of ICGA in pediatric colorectal surgery is found in Chapter 3 of this thesis.

Chapter 2

2 Rates of Anastomotic Leak, Stricture and Dehiscence Among Post-Operative Patients with Hirschsprung Disease and Anorectal Malformations: A Retrospective Cohort study

2.1 Introduction

Anorectal malformations (ARM) and Hirschsprung disease (HD) are congenital conditions affecting the colon, rectum, and or anus necessitating surgical correction. Anorectal malformations are a spectrum of diseases that encompass abnormalities in the GI tract, ranging from a blind ending rectum to a fistula to the bladder or vagina, or perineal fistula³⁷. Hirschsprung disease occurs due to a failure in caudal migration of neural crest cells, resulting in absence of ganglion cells and disordered receptive relaxation during peristalsis²⁰. Both ARM and HD require a colorectal surgery with significant dissection within the pelvis to correct. There is substantial risk of post-operative complications associated with these surgeries, including the risk of stricture, anastomotic leak, and wound dehiscence. As surgical technique and perioperative care have improved, a contemporary assessment of the rate of complications is noticeably absent from the literature.

Given the significant impact of stricture, anastomotic leak, and dehiscence on a child's wellbeing and lifetime prognosis, an informed approach to reducing these rates should be employed. We aim to determine the current rate of postoperative stricture and anastomotic leak amongst patients undergoing surgical correction of HD or ARM. In order to better classify the severity of post-operative stricture and inform future work, we propose a classification system for these postoperative complications. Lastly, we sought to assess if there were any identifiable variables associated with the development of anastomotic leak, anastomotic stricture, and anastomotic dehiscence.

2.2 Methods

This retrospective cohort study was reviewed and approved by Western REB #119479 and is reported in line with the consort statement (Appendix 1). Patients treated operatively for ARM or HD at Children's Hospital in London Ontario between January 1st, 2010, and December 31st, 2019, were included in the study. This is a convenience sample, as dates were chosen to reflect the significant change in operative management for HD and ARM in the early to mid 2000s, including uptake of laparoscopic assisted approaches. The number of cases was estimated to be ten per year of either diagnosis for a total of 100 patients, and represents a convenience sample.

Patients were identified by searching the operating room database for appropriate booking codes, namely "Anoplasty", "Anorectoplasty Posterior Sagittal", "Anorectoplasty Posterior Sagittal Laparoscopic Assisted", "Swenson Pull-Through Top End", "Swenson Pull-Through Bottom End", "Swenson Pull-Through Laparoscopic Top End". This list was generated through discussion with operating room administrative staff to determine the typical booking codes used at our institution. This list appeared to have a paucity of patients with a diagnosis with Hirschsprung disease. This was therefore supplemented by review of the local electronic health records database to identify patients via International Statistical Classification of Diseases and Related Health Problems (ICD-10) code Q43.1 for Hirschsprung Disease. Patients were included a diagnosis of HD or ARM was made by the operating surgeon, and if they underwent any of listed procedures. There were no exclusion criteria.

The electronic health record of all identified patients was then reviewed by a single clinician investigator (RW), and data were abstracted from perioperative records, operative reports, pathology reports, and other clinical documentation (e.g., discharge summary, clinic reports, etc.). Age at diagnosis and time of surgery, sex, diagnosis, medical comorbidities, presence, or absence of diverting ostomy at time of operation, and whether a diverting ostomy was created at the time of the operation were collected. The length of procedure, operative approach, (e.g., open or laparoscopic), and any note of tension, impaired vascular supply, or other intraoperative complications were noted from the operative report. Length of bowel resected, if any, was recorded from the pathology

report. Postoperative data including antibiotic regimen (choice of antibiotic and duration), perioperative steroid use (any in the week preceding or following the operation), use of non-steroidal anti-inflammatories (NSAIDs, any use within one week post-operatively), requirement for an ICU stay postoperatively, and length of stay were recorded. Data were captured for the entirety of the follow-up available through the electronic health record. There were no missing data for any of the demographic or operative variables. All patients in the cohort had at least one post-operative visit in the electronic health record.

With regards to the post-operative complications, development of stricture, anastomotic leak, and dehiscence were recorded when noted in the patient's record (e.g., discharge summary, operative report, clinic note, etc.) or met radiographic criteria.

Stricture was defined as a palpable narrowing noted by the surgeon.

Wound dehiscence was defined as description of a partial or total separation of the anastomotic edges, and pertains specifically to patients with ARM.

Anastomotic leak was defined as a defect in the anastomosis result in extravasation of bowel contents or note of extraluminal air/contrast on radiographic investigations.

Statistical analysis was conducted using Stata.BE 17.0. Data were described using means with standard deviations for normally distributed continuous variables, medians with interquartile ranges for continuous non-normally distributed variables, and frequencies with associated percentages for categorical variables. Data were compared between those who did and did not develop stricture or anastomotic leak. Univariate logistic regression analysis was conducted between patient characteristics and complications (dehiscence, leak, or stricture) using forward selection with a p-value <0.1 as threshold of significance. Our study was underpowered to perform any multivariate analysis, and therefore none were conducted.

Patients who had one or more of the complications of interest were assigned a Clavien-Dindo score⁸³. See Appendix 3 for this classification system. A novel classification system centered on describing the severity of post-operative strictures is proposed, and

patients who developed stricture were assigned a score based on the impact of the completion as described below.

2.3 Results

Our initial search of the OR coding database yielded 127 patients who underwent operative repair for Hirschsprung Disease or anorectal malformation and was then supplemented with local electronic database search of the ICD-10 code Q43.1, yielding a total of 26 patients. In total, 153 patients were evaluated for inclusion. A total of 86 patients were excluded since they did not have a diagnosis of ARM or HD, leaving 67 patients in the study cohort. Of these, 38 patients had a diagnosis of Hirschsprung Disease and 29 had a diagnosis of anorectal malformation. Table 1 demonstrates the demographic characteristics of the included population. The majority (86.8%) of HD patients were male, while sex was more evenly distributed among ARM patients (55.2% male). Mean age at time of operation was 9.1 months among HD patients and 7.3 months in those with ARM. 23.7% of HD patients also had a diagnosis of Trisomy 21 compared to only one patient with ARM (3.2%). This information and additional comorbidities are tabulated in Table 1.

Table 1: Patient demographics in retrospective review

Characteristic	HD	ARM	Total
Total (n (%))	38 (55.1)	29 (44.9)	67 (100)
Demographics			
Female (n (%))	5 (13.2)	13 (44.8)	19 (27.9)
Male (n (%))	33 (86.8)	16 (55.2)	49 (72.1)
Age at operative management (mean in months (SD))	9.1 (8.4)	7.3 (13.9)	8.3 (11.8)
Associated conditions			
Trisomy 21 (n (%))	9 (23.7)	1 (3.2)	10 (14.5)
Cardiac anomalies (n (%))	0 (0)	5 (1.6)	5 (7.2)
Tracheoesophageal fistula (n (%))	0 (0)	2 (5.1)	2 (2.9)
Renal abnormalities (n (%))	0 (0)	9 (29.0)	9 (13.0)

With respect to our primary outcome, 10 patients developed an anastomotic leak or dehiscence and 13 developed a stricture. Overall, 16 of the 67 (23.9%) patients included in the study developed one or more of the complications of interest. Amongst patients with HD (n = 38), 5 patients developed one or more complications including a postoperative stricture or anastomotic leak (13.2%). One patients developed an anastomotic leak (2.6%), and 4 developed a stricture (10.5%). In the ARM population, 11 of 29 patients developed one or more of the complications of interest (37.9%). Six ARM patients developed stricture (20.6%), while 7 suffered from wound dehiscence (24.1%). Overall, between both groups, 10.4% of patients developed an anastomotic leak or dehiscence, and 16.4% developed a stricture. These findings are summarized in Table 2.

Table 2: Summary of occurrences of anastomotic stricture, anastomotic leak, and wound dehiscence following surgical correction of Hirschsprung Disease and Anorectal Malformations

Complication	HD	ARM	Total
Anastomotic leak/dehiscence (n (%))	1 (2.6)	6 (20.6)	7 (10.4)
Stricture (n (%))	4 (10.5)	7 (24.1)	11 (16.4)
Patients with ≥ 1 complication (n (%))	5 (13.2)	11 (37.9)	16 (23.8)

After univariate logistic regression was performed assessing relationship between development of a complication of interest and sex, gestational age, and presence of diverting ostomy at time of definitive OR, no factor was found to be associated with development of a complication (Table 3).

Table 3: Proposed predictors of complications in postoperative patients with HD or ARM, univariate analysis

Variable	Odds Ratio	95% CI	<i>p</i> value
Demographics			
Sex	1.7	0.4-5.3	0.447
Gestational age at time of surgery	1.0	0.9-1.0	0.763
Operative factors			
Diverting ostomy	1.5	0.4-7.1	0.517

Table 5 summarizes the complications that occurred and provides insight into the severity of complications with provision of the Clavien-Dindo grading⁸³. A broad spectrum of consequences of post-operative stricture was noted. Therefore, a proposed classification system was created and summarized in Table 4 which links the grade of complication to the consequences.

Table 4: Proposed novel grading system for anastomotic stricture following HD and ARM or ARM repair, and their incidence among patients at our institution

Grade	Definition	HD	ARM	Total
1	Narrowing noted by surgeon, can be dilated at bedside by surgeon, resolves within two months	0	2	2
2	Narrowing noted by surgeon, can be dilated at bedside by surgeon, takes greater than 2 months to resolve	0	1	1
3	Stricture noted, unable to be dilated at bedside require sedation for dilation OR balloon dilation	3	1	4
4	Requirement for anoplasty, stricturoplasty, or ostomy due to obstructive symptoms	1	3	4

Table 5: Breakdown of complications with Clavien-Dindo Grading

Patient #	Diagnosis	Complications	Clavien-Dindo Classification	Grade of stricture, if applicable (see table 4)
1	HD	Stricture	3a	Grade 3
2	HD	Anastomotic leak	3b	N/A
3	HD	Stricture	3a	Grade 3
4	HD	Stricture	3b	Grade 4
5	HD	Stricture	3a	Grade 3
6	ARM	Dehiscence	3b	N/A
7	ARM	Stricture	2	Grade 1
8	ARM	Stricture	2	Grade 1
9	ARM	Dehiscence Stricture	3b	Grade 4
10	ARM	Dehiscence	3b	N/A
11	ARM	Dehiscence	3b	N/A
12	ARM	Stricture	3b	Grade 4
13	ARM	Stricture	3a	Grade 3
14	ARM	Stricture Dehiscence	3a	Grade 2
15	ARM	Dehiscence	3a	N/A
16	ARM	Stricture	3b	Grade 4

2.4 Discussion

A diagnosis of Hirschsprung disease or anorectal malformation can be overwhelming for a family. A plethora of questions come forward as their future workup, surgical management, and post-operative course is contemplated. Informing patients and caregivers about what to expect after diagnosis is one way to combat the unknown of what is to follow. Gathering locoregional data on rates of complications is an important part of maintaining accountability and generating hypotheses for how to improve surgical care at our individual hospital.

Of the 67 patients included in this review, 16 had a complication consisting of anastomotic leak, stricture, or dehiscence, making up 23.8% of patients. While the severity of the complications varied, as summarized in table 4, each of these patients required interventions beyond the routine postoperative course. In fact, three of these patients required urgent diverting ostomy creation, two of which were yet to be reversed more than one year after their creation. It cannot, therefore, be understated that complications can have a significant impact on HD and ARM patients, as well as their caregivers.

Specifically with regards to anastomotic leak and wound dehiscence, the rates of these complications were similar between our study and historical data. Our HD patients had a 2.6% risk of anastomotic leak compared to historical rate of 1.7%⁸⁴. Among ARM patients, the rate of dehiscence was 20.6% (6 patients) at our centre compared to 31% from a 2018 study from Sweden⁸⁵. Three of these patients developed pelvic sepsis requiring emergent washout and extended antibiotic use, making up 10.3% of ARM patients, compared to 10% quoted in the study.

Stricture was the most commonly occurring complication that was studied. Among patients with Hirschsprung Disease, 10.5% developed a stricture compared to the historical average of 11%⁸⁶. 24.1% of ARM patients in our study developed stricture compared to previous studies that demonstrated a range of 4.8-30%^{54,87}. Stricture was defined as a palpable narrowing on DRE by the surgeon, however it became clear during literature review that post operative stricture can have a wide range of severity. Treatment

for a stricture may be simply performing bedside dilations of the anastomosis for one to two months post operatively, or as severe enough to require urgent diverting ostomy, anoplasty, or stricturoplasty. There does not appear to be a classification system in the literature to date that can more accurately describe the severity of and extent to which a postoperative stricture impacts the patient. As such, we propose the classification system shown in Table 4 to address this gap. Knowing the approximate rates of these grades of stricture can help us communicate a more accurate postoperative course.

There is a clear association between trisomy 21 and Hirschsprung disease, however there is mixed data on how Trisomy 21 may impact the postoperative course¹⁵. Historically it was believed that patients with HD and Trisomy 21 are at higher risk of enterocolitis⁸⁸. However, a retrospective study investigating the rate of enterocolitis and overall bowel function in HD patients with and without Trisomy 21 was performed in 2016 and suggested no increased risk of enterocolitis⁸⁹. With regards to anastomotic leak and stricture, there is no current evidence for an increased risk among patients with Trisomy 21 and HD. Among patients with ARM and Trisomy 21, studies have demonstrated no significant difference in postoperative complications compared to those without Trisomy 21⁴⁷. There is, however, a tendency towards functional constipation among these patients⁴⁷. Since investigation into the rates of stricture and anastomotic leak among these patients has not been thoroughly studied, it warrants further investigation such that we can better inform patients and their families. The results of our study agree with the current literature, and in fact none of the patients that developed anastomotic stricture, leak, or dehiscence had a co-diagnosis of Trisomy 21.

Gestation adjusted age at time of repair has been shown to have an impact on rates of anastomotic stricture and leak among patients with HD⁹⁰. A multicenter study from 2017 suggest a significant increase in these complications when HD correction is performed at less than 28 days of age⁹¹. For patients with ARM, timing of repair depends on the individual patients' anatomy and co-morbidities. Our analysis did not reveal a statistically significant relationship between age at time of operation and the complications of

interest. This likely is reflective of the locoregional practices of our surgeons, preferring not to operate on premature infants.

Equipped with more specific locoregional data, it is evident that there is room for improvement in reducing rates of stricture, leak, or dehiscence. Approximately 1 in 4 patients sustained one of these complications, with half of those being classified as a Clavien-Dindo 3b. There have been attempts to search for predictors of developing stricture, leak, or dehiscence, which has identified that presence of a diverting ostomy during healing after repair of ARM may reduce the rate of dehiscence. Considering these previous studies, univariate logistic regression was performed to identify any potential relationship between gestation-adjusted age at time of surgery, sex, and open versus laparoscopic approach. While the influence of preoperative and postoperative antibiotic use, as well as NSAID use have been implicated in complication rates in the past, the practice of our surgeons was essentially uniform with regards to these variables (almost every patient received at least a 3 day-course of antibiotics and had routine ibuprofen given).

None of the tested variables appeared to have any association with the outcomes of interest in this study. While this may in part be due to limited numbers of patients included, this is supported by the literature. This once again raises the possibility that development of these complications may be due to operative factors not easily assessed by conventional means. A prominent theory behind anastomotic leak, stricture and dehiscence is insufficient vascular supply leading to ischemia of the anastomosis. Both ARM and HD correction require pelvic dissection and a form of pull-through procedure in the pelvis, so palpation for a pulse, peristalsis, and proximal mucosal colour is difficult in this region. This raises the question of the utility of intraoperative adjuncts for ensuring adequate vascular supply to the anastomosis to ideally reduce the rates of these complications.

Small patient numbers are one of the main limitations of this study. There may have been patients missed in the record identification process, potentially excluding patients that may have otherwise been eligible. While a significant percentage of patients did have one

of the outcomes of interest, the overall low incidence of complications (<10 occurrences in HD patients) limited the ability to perform multivariate analyses. Additionally, this data was collected retrospectively and relied upon documentation by the clinical team at the time for several variables of interest, thus introducing potential information bias.

Overall, the greatest limitation to this review was limited sample size. The study was conducted based on a sample of convenience, and to reflect the fact that in 2010 a significant change in practice occurred that would render results from before this time difficult to interpret. For these reasons, multivariate modelling was not possible, particularly with the aim to identify modifiable risk factors. Instead, the associations between patient level risk factors and outcomes were investigated using bivariate modeling, and were considered only hypothesis generating. While no associations were identified, this does not mean that they do not exist. This study is underpowered to detect these associations and further research is warranted.

Moving forward, steps have been made to create a national database in conjunction with the Canadian Consortium for Research in Pediatric Surgery (CanCORPS). The project has been adopted by the group and data acquisition at a number of Canadian institutions should be underway in 2023. This study sample size is based on the desire to complete multivariable analysis to identify risk factors associated with complications. Based on the rule of thumb of at least one event per variable included, we will include 750 patients which – assuming a conservative 20% complication rate – will allow for 15 variables in multivariable analysis. Further, while the rates of complications were similar in this study compared to the literature, this larger study could reinforce these rates to make a sample size for the RCT in Chapter 4 more accurate.

2.5 Conclusion

Overall, the rate of stricture, anastomotic leak, and anastomotic dehiscence among our center's postoperative Hirschsprung Disease and Anorectal Malformation patients is similar to that in the historical literature. We did not identify any demographic or operative factors that may lead to development of these complications. This lends credence to the notion that intraoperative factors such as tension and adequate blood supply are key contributors to stricture, leak, and dehiscence. This study also identified a gap in terminology to describe the severity of post-operative stricture. Since nearly a third of patients after ARM developed significant stricture requiring some form of intervention, it is important to characterize the degree of ongoing stricture-related care these patients require and the proportion of patients that fall into each category. Future directions for this study include expansion into a multi-centered review to garner improved statistical power. Development of a national database on postoperative complications following repair of HD and ARM could address the difficulties in performing adequately powered studies in patients with rare diseases.

Chapter 3

3 The Use of Indocyanine Green Angiography in Pediatric Colorectal Surgery: A Systematic Review

3.1 Introduction

Indocyanine green (ICG) is a water-soluble dye first used in human subjects in 1957⁶⁷. The ability of ICG to bind to blood plasma proteins and fluoresce under near-infrared (NIR) light, coupled with its very low side-effect profile made it an ideal tool in assessing vascular supply to a variety of tissues⁶⁸⁻⁷⁰. When a solution of ICG dissolved in water is injected intravenously, it is rapidly distributed throughout the body, and when excited with NIR and visualized with a specialized camera with filter, tissues with adequate vascularity fluoresce. Initially used in studies of hepatic flow and ophthalmology in the 1960s, its uses have multiplied, from graft perfusion assessment in plastic surgery, to confirmation of adequate aneurysm clipping in neurosurgery^{75,81,92}.

Like many medical technologies, ICG was first studied in adults. Over time, ICG has been trialed in a variety of pediatric surgical procedures. Lau *et al* published a review of its applications in pediatric surgery in 2019, with an overview of its use in hepatobiliary surgery, cholecystectomy, varicocele repair and other urologic operations, as well as hepatoblastoma resections and thoracic surgery⁸¹. One common use of ICG in adult general surgery was missing from this review, namely, to assess vascularity of bowel during colorectal surgery.

In the adult literature, ICG use appears to be associated with a lower rate of anastomotic leak, particularly during rectal resections for colorectal cancer surgery⁷⁶. Hirschsprung disease, anorectal malformation, rectal prolapse, and inflammatory bowel disease are a few of the conditions affecting the pediatric population that may require operative management with colorectal resection and anastomosis. Little data exists on the use of ICG during pediatric colorectal pull-through surgery to determine if it could also provide similar benefits as the adult population.

We undertook this study to determine if the use of ICG in pediatric colorectal surgery reduces the rate of post-operative complications. Considering indocyanine green angiography has shown promise in reducing rates of anastomotic leak in adult populations, assessing if there is any impact on complications in pediatric populations in the existing literature is the first step in investigating this technology.

3.2 Materials and Methods

This review follows PRISMA guidelines and was registered with PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=275251). We conducted a comprehensive literature search using Ovid Embase, Ovid MEDLINE, and Web of Science databases with the assistance of a medical librarian. The search was conducted in September 2021. Key search terms included “pediatric”, “child”, “adolescent” and “colon”, “rectum”, “colorectal”, “surgery” and “complications”, “anastomosis”. For full details on search strategy see Appendix 2.

Covidence Systematic Review Management software (Veritas Health Innovation, Melbourne, Australia) was used to aid in the management and evaluation of the literature. Abstracts were compiled and deduplicated. Two reviewers screened all title and abstracts, and full texts were obtained for any abstract identified as potentially relevant by either reviewer. Studies were considered for inclusion if they reported on pediatric patients (age < 18 years), were published in the peer reviewed literature, and reported on surgery of the colon or rectum with ICG used for angiographic purposes. Studies were excluded if they were published in abstract form only or were not available in English. Each reviewer then evaluated full texts for eligibility and performed data extraction for studies meeting eligibility criteria. Disagreement between reviewers was resolved by discussion and consensus. *A-priori* we determined that data synthesis would only occur if >10 studies evaluated a single outcome. No limits were placed on study methodology. The reference lists for all studies that underwent full text review were screened for additional papers that may meet criteria, for which there were none.

Data extracted for each study included: title; study design; time frame; date of publication; any funding sources identified; stated conflicts of interest; number of patients; patient demographics; diagnoses; operative details; detail of IGCA and any change in management; complication of ICG; post-operative complication; and any objective measurement of ICGA perfusion assessment presented. No additional data were obtained from study authors to supplement published results.

All identified studies were observational in nature. A risk of bias assessment was performed by two reviewers (RW and BS) using the Joanna Briggs Institute Checklist for Case Series and Case reports, where appropriate (Joanna Briggs Institute, 2017)⁹³.

3.3 Results

3.3.1 Results of literature-based search

The initial search yielded 204 deduplicated studies abstracts and titles. Figure 4 demonstrates the flow of studies. After preliminary review, 197 were excluded at the abstract screening stage due to not meeting inclusion criteria (not in pediatric population, or wrong intervention (e.g., not involving colorectal surgery)) leaving 8 studies appropriate for full-text review. 5 further studies were excluded, one of which was only published in abstract form, one manuscript had not undergone peer-review, two were within the adult population, and one employed ICG during small bowel resection. Three studies remained that met all inclusion criteria and no exclusion criteria.

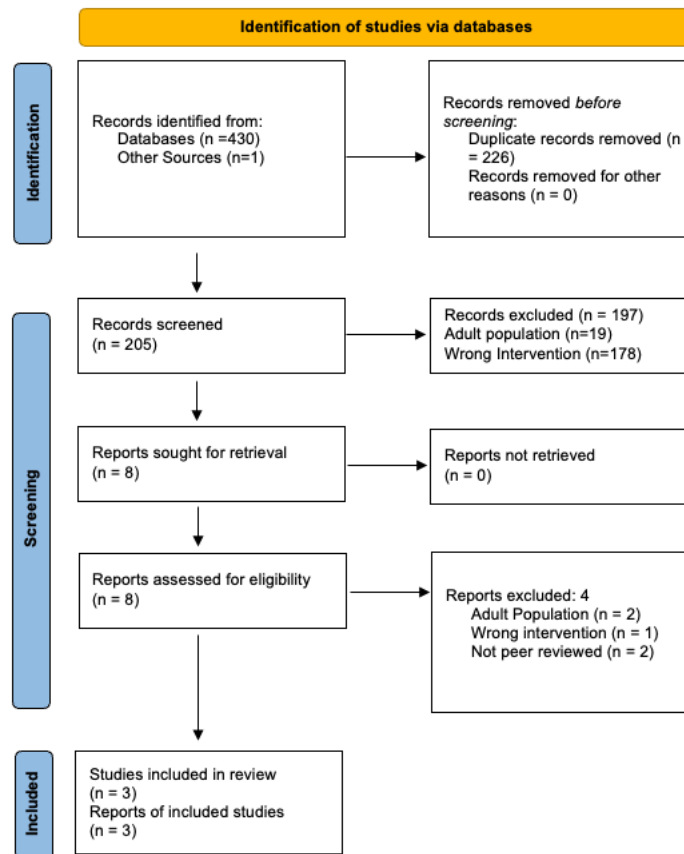


Figure 4: PRISMA Flow Diagram

3.3.2 Study characteristics

Table 6 summarizes the study characteristics and results. One study was a case report⁹⁴, and the other two were case series including 2⁸⁰ and 13 patients⁸² respectively. The patients ranged in age from 6 months to 17 years. One patient (17 years of age) underwent an Altemeier procedure for rectal prolapse⁹⁴. With respect to procedure: Two patients underwent closure of colostomy⁸⁰; 1 underwent a pull through and 2 a re-do pull-through, 8 underwent a posterior sagittal anorectal vaginal urethralplasty (PSARVUP), and 2 a re-do PSARVUP; 2 underwent an anoplasty, and one anoplasty revision⁸².

Table 6. Study characteristics and operative descriptions

Study	Study Design	n Patients (%Female)	Surgery (n)	Diagnosis (n)	ICG dose	ICG technique	Impact on course (% cases)
Yamamoto et al., 2021 (Japan)	Case Report	1 (100)	Altemeier (1)	Rectal prolapse (1)	0.2 mg/kg	Unspecified	0
Yada et al., 2020 (Japan)	Case Series	2 (50)	Colostomy closure (2)	Rectal atresia post-PSARP, unwanted colostomy (1) Rectovestibular fistula post-PSARP, unwanted colostomy (1)	0.3 mg/kg	Stryker PINPOINT – ICG diapogram	0
Rentea et al., 2020 (USA)	Case Series	13 (77)	Re-do pull-through (2) PSARVUP (8) Redo PSARVUP, creation neo-vagina (1) Primary pull-through (1) Colonic pull-through (1)	Cloaca (9) Rectal atresia – ARM (1) Hirschsprung Disease (3)	0.1-0.3 mg/kg	ICG-FA SPY Elite Imaging system	31

3.3.3 Study results

With respect to the primary research question, the observational studies identified in this search did not yield comparison data on whether ICGA is associated with a reduction in post-operative complications. All three studies made a comment on whether complications had occurred, but the definitions and follow up period were not specified in the Yada and Yamamoto studies^{80,94}. The Rentea study reported only one post-operative complication of anoplasty dehiscence requiring revision, and they reported no long-term strictures occurred. However, separately they stated two patients had a stricture dilated with mitomycin during an examination under anaesthesia at the 6-week post-operative mark, and 2 patients required subsequent stricturoplasty⁸². The only long-term outcome reported by Yamamoto was that there was no recurrence of rectal prolapse at 18 months after surgery⁹⁴. Likewise, Yada reported that “no post-operative complication occurred after discharge”⁸⁰.

The dose of ICG was within the range of 0.1-0.3 mg/kg across the studies. None of the studies stated a re-dosing of ICG was required. While specific timing of injection to visualization of ICG was not stated in two of the studies^{82,94}, Yada et al⁸⁰ noted good quality of perfusion at the 30 second mark following administration. None of the studies described any adverse effects of ICG administration. Rentea reported three patients that required intraoperative vasopressor use, one before ICG administration and two after ICG administration. An attempt at quantitative assessment was made in one of the three studies captured in this review. Time to visible fluorescence (<30 seconds as cut-off) and subjectively comparable intensity to control area was used by Yada et al⁸⁰. Rentea et al described visual inspection and perfusion intensity without an assignment of a numeric score⁸². All three studies commented on whether a change in management occurred, which was the case in 4/13 subjects in the Rentea study, or 31% of cases performed. No change in operative management occurred during operations performed in the Yada and Yamamoto studies^{80,94}.

An additional application of ICG was performed by the Yada study⁸⁰. A “diapogram” was performed to assess for return of bowel function in the two patients included in their case series. They noted ICG present mixed with stool with use of the handheld camera.

3.3.4 Risk of Bias

The results of the JBI checklists are tabulated and found in Tables 7 and 8. All included studies had a high risk of bias.

Table 7: JBI Critical Appraisal Checklist for Case Series

Study	Were there clear criteria for inclusion in the case series	Was the condition measured in a standard, reliable way for all participants included in the case series	Were valid methods used for identification of the condition for all participants included in the case series	Did the case series have consecutive inclusion of participants	Did the case series have complete inclusion of participants	Was there clear reporting of the demographics of the participants in the study	Was there clear reporting of clinical information of the participants	Were the outcomes or follow up results of cases clearly reported	Was there clear reporting of the presenting site(s)/clinic(s) demographic information	Was statistical analysis appropriate
Rentea ⁸²	Yes	Unclear	Unclear	No	No	Yes	Yes	Yes	No	Not Applicable
Yada ⁸⁰	No	Yes	Unclear	No	No	Yes	Yes	Yes	No	Not Applicable

Table 8: JBI Critical Appraisal Checklist for Case Report

Study	Were patient's demographic characteristics clearly described	Was the patient's history clearly described and presented as a timeline	Was the current clinical condition of the patient on presentation clearly described	Were diagnostic tests or assessment methods and the results clearly described	Was the intervention(s) or treatment procedure(s) clearly described	Was the post-intervention clinical condition clearly described	Were adverse events (harms) or unanticipated events identified and described	Does the case report provide takeaway lessons
Yamamoto ⁹⁴	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes

3.4 Discussion

This systematic review yielded three studies which employed ICGA in pediatric colorectal surgery. This reflects the paucity of reported uses of indocyanine green angiography (ICGA) in pediatric colorectal surgery. It does, however, reveal that ICG has been employed relatively successfully and without major complications for several indications, namely during Altemeier perineal rectosigmoidectomy, colostomy closure, primary and re-do PSARVUP, and primary and re-do colonic pull-through. With regards to the primary research question, none of these studies were able to address if ICGA impacts the rate of post-operative malperfusion-related complications.

There was one report of an anoplasty dehiscence in the Rentea study, as well as two patients requiring stricturoplasty⁸². The protocol for detecting post-operative complications was not specified by the other two studies, limiting our ability to assess for incidence of outcomes of interest. The finding of 31% of patients in the Rentea study receiving additional bowel resection following ICGA is an interesting observation⁸². This is higher than in the adult literature, with a meta-analysis of ICG during oncologic resections yielding a change in operative plan 16.4% of the time⁹⁵. This is likely since it is a retrospective study of the cases which employed ICGA during ARM and HD repair, with selection of patients not standardized and based on surgeon preference. This may reflect a bias towards selection of patients in which concerns about the anastomotic perfusion were already present.

An attempt at quantitative assessment was made in one of the three studies captured in this review. Time to visible fluorescence (<30 seconds as cut-off) and subjectively comparable intensity to control area was used by Yada et al⁸⁰. Quantitative evaluation of fluorescence for determination of perfusion continues to be a point of investigation, although there is no clear consensus on the best tool to achieve this⁹⁶. A systematic review by Slooter et al published in 2021⁹⁶ identified four main cited metrics for objective measurement of tissue perfusion, including 1. time to fluorescence, 2. contrast-to-background ratio, 3. pixel intensity and 4. numeric classification scale. Furthermore, 9 of the 23 studies included in this review were animal studies, and only 15 of the 23 were concerning lower GI surgery. Overall, the conclusion of the author considered time to

fluorescence as the most easily adoptable metric. This systematic review highlights that even amongst the adult literature, objective assessment of fluorescence intensity has not been standardized or adopted widely, and the current metrics are yet to be validated in pediatric patients.

The dose of ICG delivered was similar across the three studies and were within the range suggested within the ICG product monograph⁹⁷. Additionally, there were no reports of re-dosing of ICG during any of the operations conducted across the studies, indicating that this may be a reliable dose range in pediatric populations for this indication.

The performance of a diapogram by the Yada study is an interesting application of the technology. Theoretically, since ICG is excreted through the biliary tract and into stool, the presence of ICG in the stool confirms that the stool in the post-operative diaper has traveled the length of the digestive tract since the time of surgery.

Limitations of this study include the lack of grey literature search, and the fact that primary authors were not contacted for more information with regards to the outcomes of interest. The risk of bias assessment performed on each study demonstrated that they are all at high risk of bias, limiting the ability to interpret the results in a more generalizable way. Additionally, the small number of studies included limited any ability to perform a meta-analysis.

In order to make this review more comprehensive in capturing the current uses of ICGA in pediatric colorectal surgery, a scoping review should be conducted in future. To make this more inclusive, the search should not be limited to English language, and a grey literature search should be conducted. Considering the novelty of this technology, it may be necessary to continue to include studies of varying design depending on the results of this more extensive search. This type of search may still preclude the ability to perform a meta-analysis given heterogeneity, but would likely capture more completely the applications of ICGA to date.

Published literature found during this review remains underpowered to detect a difference in malperfusion-related complications following colorectal surgery in pediatrics.

Bolstered by strong results of an odds ratio of 0.39 for reducing rate of anastomotic leak in adults⁷⁶, further research will be required to investigate this promising intervention further while minimizing potential for bias intentionally within the study design.

Chapter 4

4 Indocyanine green angiography in pediatric colorectal surgery: A feasibility randomized controlled trial

4.1 Introduction

Hirschsprung Disease (HD) and Anorectal Malformation (ARM) are congenital conditions affecting approximately 1 in 5000 live births worldwide^{37,98-100}. Both conditions affect the most distal portions of the gastrointestinal tract, namely the colon, rectum, and/or anus. ARM and HD are also similar in the surgical approach to their correction – a pull-through procedure in which healthy bowel is brought down to the anal verge.

Both ARM and HD repair are at risk of complications. Among these are anastomotic stricture, in which a rim of fibrotic tissue forms where the bowel was sutured to the anal or neo-anal verge. This is particularly common in postoperative ARM patients, with the literature quoting rates of 6-30%⁸⁷. It is also prevalent in post-HD repair patients with rates of 6-14%¹⁰¹. Anastomotic strictures can result in functional disorders of stooling and can be severe enough to cause obstruction, occasionally requiring repeat surgery. Wound dehiscence and anastomotic leak are somewhat interchangeable terms in these cases, as both describe the anorectal anastomosis coming apart. “Dehiscence” is used to refer to this phenomenon in patients with ARM given the superficial nature of the anastomosis, while “leak” is used for patients with HD as this is more conventional in the literature, and the anastomosis is located deep to the skin. Leak or dehiscence may result in increased pain, cosmetic consequences, or local wound infection, but can also be as severe as intrabdominal infection if there is leakage of stool into the abdominal cavity. The incidence of anastomotic leak historically among post pull-through patients with HD is in the realm of 1.5-8.0%^{101,102} while post-ARM correction patients have dehiscence in up to 35% of cases⁸⁵.

Previous studies have demonstrated a link between colonic malperfusion and anastomotic leak, stricture, and wound dehiscence^{103,104}. In the case of both HD and ARM, after resection, reconstruction involves anastomosing the colon to the anus. The adult literature

emphasizes the association between location of anastomosis and anastomotic leak, namely the more than double risk following colorectal anastomosis (6.7%) versus colocolonic anastomosis (2.6%)¹⁰⁵. Several studies in adult literature have shown that the lower the anastomosis, the higher the risk of anastomotic leak¹⁰⁶⁻¹⁰⁸. It is postulated that the deficiencies in blood supply to the anastomosis (anastomotic perfusion) is a primary driver for these complications, and the technical aspect of deep pelvic surgery makes ensuring adequate perfusion more difficult. The location of dissection, and difficulties in employing conventional methods of anastomotic perfusion assessment (colour of the bowel, peristalsis, palpation of a pulse, and bleeding edge to assess vascular supply) deep within the pelvis, make HD and ARM particularly prone to ischemia-related complications. This reinforces the notion that operations for correction of HD and ARM are particularly poised to gain benefit from ensuring adequate perfusion.

Considering the link between poor vascular supply and these complications, any technique that can assist in assessing blood flow to the anastomotic site would be desirable. Indocyanine green angiography (ICGA) may be such a technique. ICGA has been applied to many pediatric surgical procedures across specialties^{81,109,110}. It has not yet been thoroughly evaluated in pediatric colorectal surgery, however, has been studied much more in adult colorectal surgery²²⁻²⁴. ICG is a water-soluble dye that binds to plasma proteins in the blood and is excreted through the hepatobiliary system⁷⁰. When bound to plasma proteins, it can absorb near infrared (NIR) light, and emit wavelengths visible after passing through a filter before projection on a monitor⁶⁹. In the case of colorectal surgery, this allows the surgeon a more objective measure of perfusion to the bowel to be anastomosed, or to the anastomosis itself. ICGA has been applied during low anterior resections, oncologic dissection, and other applications during adult colorectal surgery. Randomized controlled trials and subsequent meta-analyses have been conducted in these populations and suggest there may be a decreased rate of anastomotic leak due to the addition of this more objective measure of anastomotic perfusion^{92,111,112}.

Given the success of ICGA in adult colorectal surgery, we hypothesize there may be a role for ICGA in the prevention of complications after surgical repair of HD and ARM. We therefore undertook this study to determine the feasibility of conducting a

randomized controlled trial evaluating the use of ICGA vs. standard operative intervention in children undergoing surgical repair of HD or ARM with respect to post-operative anastomotic complications.

4.2 Materials and Methods

We obtained Health Canada Approval for this study pertaining to ICG use in pediatric colorectal surgery (control number 251727), as well as local hospital ethics approval (REB# 118568). We conducted a single-center feasibility randomized controlled trial, and the trial protocol was registered in advance (ClinicalTrials.gov Identifier: NCT04904081). All patients under the age of 8 years diagnosed with and being treated operatively for Hirschsprung disease (HD) or anorectal malformations (ARM) at a single tertiary care hospital over a one-year period were approached for recruitment between June 2021 – May 2022. Patients were considered eligible if they met the following inclusion criteria and none of the exclusion criteria:

Inclusion criteria

- 1) Hirschsprung's disease or anorectal malformations, diagnosed by all the following:
 - a. Clinical evaluation and physical examination
 - b. Radiologic studies including abdominal x-rays and/or contrast enemas
 - c. Pathologic diagnosis after rectal biopsies (HD only)
- 2) Age greater than one-month of age to 7 years at the time of surgery
- 3) Planned to have surgical management for their diagnosis
- 4) Substitute decision maker (SDM) able to read/write/understand English

Exclusion criteria

- 1) Patients with a known iodine allergy

Potentially eligible patients were identified by pediatric surgeons evaluating patients with HD or ARM at Children's Hospital, London Health Sciences Centre. Additionally, a member of the research team reviewed clinic lists on a weekly basis to identify eligible patients. Patients were approached for inclusion during a pre-operative consultation

appointment by the project research assistant or other member of the research team. Once consent was obtained, the patient was randomized through a secure online portal using a computer-generated randomization sequence in a 1:1 allocation ratio. The randomization sequence was stratified based on diagnosis (ARM or HD) to ensure balanced representation of these conditions in both the intervention and control groups. Randomization occurred at the time of consent to facilitate availability of ICG and associated equipment on the day of surgery if the patient was randomized to the intervention arm.

Patients in the intervention arm of the trial received standard of care surgical procedures according to surgeon preference, with the addition of ICGA. Once the surgeon had performed the resection of bowel and was prepared to create the colo-anal anastomosis, ICG was administered in a dose of 0.2 mg/kg intravenously by the attending pediatric anesthesiologist, and the patient was monitored for any adverse reactions (hypotension, desaturation, etc.). Perfusion of the bowel was then observed using the hand-held Stryker NIR camera. Subjective assessment of the bowel perfusion was performed by the operating surgeon, and when determined to be adequate, completion of the anastomosis was performed. A member of the research team was present to record any changes in decision making (e.g., further resection of bowel) based on the results of ICGA. Patients in the control arm received standard of care surgical procedures according to surgeon preference, with standard intraoperative monitoring by the anesthesia team.

Participants and their caregivers were blinded to intervention status. Due to the nature of the study, surgeons were unable to be blinded to allocation. Except for the use of ICGA, care provided to both groups was left to the discretion of the surgeon. Follow up consisted of standard post-operative follow-up occurred i.e., daily visits by the surgeon and team during hospitalization followed by an outpatient postoperative clinic visit at 2-4 weeks with remainder of follow-up determined by the surgeon based on the patient's condition. Patients were evaluated for postoperative complications including stricture, leak, and dehiscence based on review of operative records, discharge documentation and clinical follow-up records. Surgeons were contacted directly for clarification when required.

The primary outcome of this feasibility trial was the proportion of eligible patients recruited over the study period. *A-priori*, we set a cut-off of 80% of eligible patients recruited to support eventually proceeding to a larger RCT. Acceptability of randomization and procedures were measured by assessing retention/loss-to-follow up. Subjective opinion of surgical staff on whether they found the ICGA useful in anastomotic evaluation was also asked and recorded.

Secondary outcomes included incidence of anastomotic leak, wound dehiscence, anastomotic stricture, reoperation rate, and readmission rate, as well as incidence of any complications from ICG use (i.e., anaphylaxis). Stricture was defined as a palpable narrowing noted by the surgeon on digital rectal examination. Wound dehiscence was recorded when noted by clinical staff, pertaining to ARM patients. Anastomotic leak was recorded when clinical staff documented occurrence, or imaging investigations noted free air or contrast extravasation from anastomotic site.

Based on historical data, we anticipated 10 patients with ARM or HD would be treated at our facility over the study period and therefore at least 8 would form our convenience sample. Since this is a feasibility study, no conclusions on the effectiveness of ICGA compared to standard care were made. Analyses are descriptive in nature, with normally distributed continuous data presented as means with standard deviations, non-normally distributed continuous data presented as medians with maximum and minimum values given the small sample size, and categorical data presented as frequencies with associated percentages.

4.3 Results

10 eligible patients were identified for consideration, of whom eight (80%) were consented for study enrollment over the 12-month study period (Figure 5). One patient who was not consented was upon request of the operating surgeon. The other patient who did not consent refused enrollment in the study for unclear reasons. Another patient withdrew consent on the day of study in part due to apprehensions from another caregiver who was not present during the initial recruitment process.

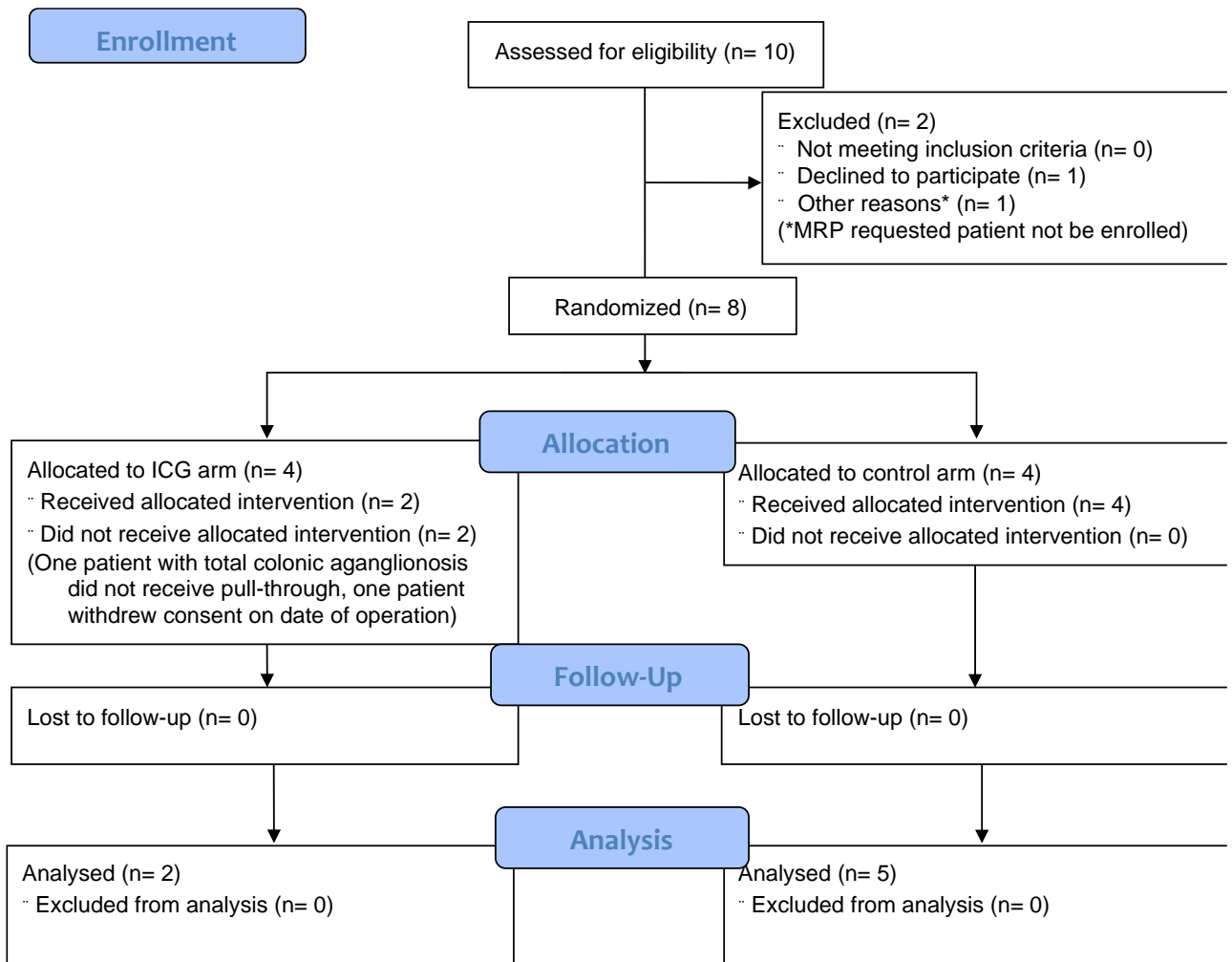
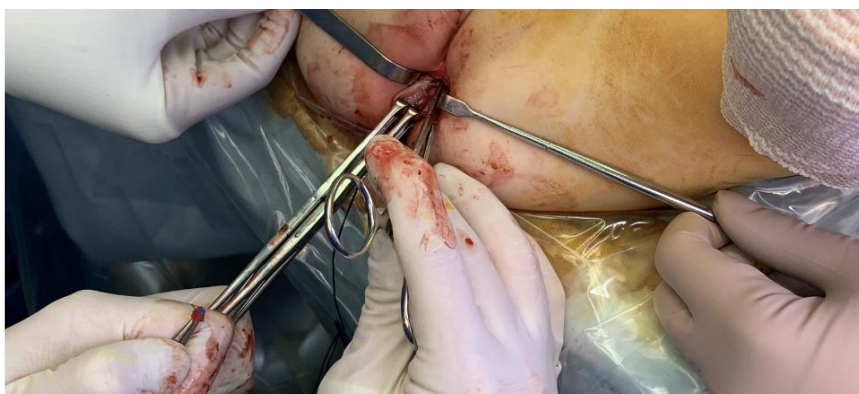
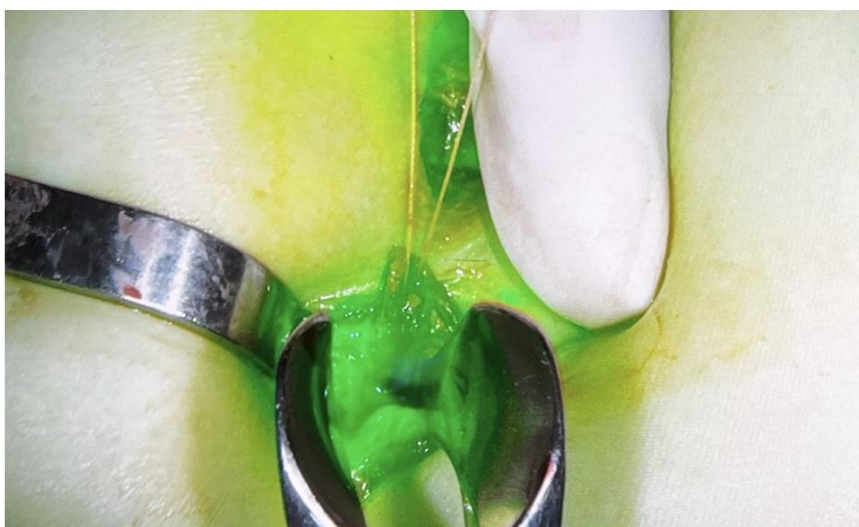


Figure 5: Enrollment flow diagram, CONSORT 2010

Demographic details of the included patients can be found in Table 9. Within the ICG group, 50% of patients had a diagnosis of HD, and 50% had a diagnosis of ARM. The control group was composed of 75% ARM and 25% HD. There were no reported concerns with feasibility of ICGA, and no patients were noted to suffer a complication from ICG administration. Median operative time was 295 minutes in the ICGA group (range 147 – 525 minutes) and in the control group was 285 minutes (range 212 – 357 minutes). When operating surgeons were asked if they found the ICGA useful, they responded in the affirmative. Intraoperative photographs with permissions are seen in Figure 6.



Identification of anastomotic site prior to ICG administration



Proposed anastomotic site after ICG visualized with handheld camera

Figure 6: Intraoperative photographs, before and after ICG

Table 9: Demographics of included patients

Variable		ICGA Group	Control Group
Diagnosis	HD, n (%)	1 (50)	1 (25)
	ARM, n (%)	1 (50)	3 (75)
Sex (% female)		50	25
Weight (kg (min-max))		6.7 (5.7-7.7)	9.1 (5.2 – 17.3)
Age at time of correction (median days (min-max))		171 (89-252)	138 (113 – 2,489)
Medical comorbidities (n)	Trisomy 21	1	1
	Townes Brocks syndrome	0	1

In each group, an instance of stricture and dehiscence occurs. In the ICGA group, both the stricture and dehiscence occurred in the same individual with ARM and required two additional operations for examination under anesthesia (EUA) and dilation of stricture. Please refer to Table 4 in Chapter 2 for more information on the proposed grading system of post-operative strictures. In the control group, the stricture occurred in a patient with HD, and likewise required two EUAs with dilations of the stricture. The patient with dehiscence in the control group was managed conservatively without operative intervention. These results are summarized in Table 10.

Table 10: Perioperative details

Variable	ICGA	Control Group
Median operative time (minutes (min-max))	295 (147-525)	285 (212-357)
Length of stay (days (min-max))	5.0 (4-6)	6.5 (3-9)
Post-operative stricture	1 (grade 3)	1 (grade 2)
Post-operative anastomotic leak	0	0
Post-operative dehiscence	1	1

4.4 Discussion

The study presented here represents an important step towards completion of a randomized controlled trial to determine the efficacy of ICGA in reducing post-operative anastomotic complications in patients undergoing surgical repair of HD and ARM. In this single centre, feasibility RCT, we demonstrated the ability to recruit 80% of patients approached for trial enrollment. This met our pre-specified threshold to proceed with a multicenter RCT to address a clinically relevant question: does the addition of ICGA to standard care result in a decrease in the rate of perfusion-related postoperative complications?

A retrospective study at our center revealed that approximately 25% of patients at our institution develop a potentially malperfusion-related complication (stricture, leak, or dehiscence) following operative repair of HD or ARM. There is clear value in striving to reduce the risk of developing these complications as they can have severe long-standing impact. Recognizing the difficulties encountered in performing randomized controlled trials among pediatric patients with rare diseases and adjusting the corresponding protocol accordingly is imperative to ensure trial feasibility.

Both the ICG and the control groups had one occurrence of anastomotic stricture and dehiscence, while the stricture and dehiscence in the ICG group occurred in the same individual. This provides evidence that the protocol was able to detect the secondary outcomes of interest but should not be interpreted in terms of correlation with ICGA due to the small number of patients. Additionally, while operative time is an important consideration when assessing if this new technology is feasible, the range of operations performed varied significantly based on operative factors beyond ICGA use. The true additional operative time attributable to ICG would hopefully be elucidated in a larger trial. Similarly, the demographic skew towards male patients noted in this study would likely be less dramatic on a larger scale but may also reflect the 4:1 male preponderance for HD¹³.

With regards to the question of feasibility of performing a trial using ICGA in pediatric patients, this trial demonstrated our ability to recruit 80% of patients. Sample size based

for a future multi-center randomized controlled trial for ICG with the aim at reducing postoperative complications was calculated. This required extrapolation of adult data, which has suggested an Odds Ratio of 0.39 for anastomotic leak when ICG was used for colorectal surgery based on a meta-analysis performed in 2021¹¹¹. The composite incidence of anastomotic stricture, leak, and dehiscence was estimated at 25% based on results from our retrospective review (see Chapter 2). With these metrics, a power of 0.8, and alpha set at 0.05, a sample size of 192 patients would be required with 96 patients in each arm.

Additionally, as a metric for feasibility, acceptability of randomization and procedures was measured by assessing retention/loss-to-follow up. Since no patients were lost to follow up, the acceptability of randomization and procedures appears to be excellent. This can be attributable to the fact that administration of ICG intraoperatively does not require any additional effort on the part of patients or their caregivers. The willingness of clinicians to recruit patients did impact the recruitment process in one instance. Qualitative feedback on reasons the clinician did not want to participate consisted of a sense that the patient's family was overwhelmed by their diagnosis at baseline. Two families declined to enter the study, and an additional family withdrew on the date of surgery. This may suggest limitations in the consent discussion's approachability and could be improved upon with provision of interactive resources to enhance the consent discussion. As another metric of feasibility, it was found that blinding of patients and their families was feasible. As previously highlighted, blinding of the surgeon is not possible due to the nature of the intervention.

Limitations of this study include that secondary outcome data was not collected while patients were in hospital. To reduce the risk of information bias, a future trial may collect this information prospectively. Due to the nature of the intervention, the operating surgeon was unable to be blinded to the allocation. Additionally, the camera equipment (laparoscopic or hand-held) may not be available at all institutions. In our institution, this required adequate advanced notice with equipment representatives to ensure all necessary equipment was available for the day of surgery. This made it necessary to randomize patients well in advance of the subject's surgery date. There is, however, a trend towards

uptake of modern equipment with ICG capabilities in Canada, lending hope that the necessary materials will be available at pediatric surgery centers.

Overall, the study protocol was found to be feasible in the employment of ICGA during pediatric colorectal surgery. Anecdotally, ICG was found to be a useful adjunct to assessing anastomotic viability. The roll-out of this protocol in a multi-center randomized controlled trial would be a valuable step in determining a relationship between ICG use and incidence of ischemia related complications such as anastomotic leak, dehiscence, or stricture.

Chapter 5

5 Conclusions and future directions

5.1 Summary

This thesis sought to evaluate the indication for and potential use of indocyanine green angiography (ICGA) in pediatric colorectal surgery. A series of steps were conducted to determine its role in operative management of Hirschsprung Disease (HD) and Anorectal Malformations (ARM). Firstly, a retrospective review of our institutions complication rates among these patients was conducted. Secondly, a systematic review was conducted to discover how ICGA has been employed in pediatric colorectal surgery thus far. Lastly, a feasibility randomized controlled trial was conducted to assess the viability of a multi-centered trial.

5.2 Retrospective study conclusions

The retrospective review conducted between 2010 and 2019 revealed that there remains an unacceptably high rate of complications among patients following repair of HD and ARM. Approximately 25% of patients developed a postoperative anastomotic stricture, leak, or dehiscence, often requiring reoperation. An attempt was made to determine if there were any perioperative factors that influence the development of these complications, such as patient sex or gestational age, but no clear associations were found. This emphasizes the importance of optimizing operative factors such as perfusion to the anastomosis, which is postulated to be associated with these complications.

5.3 Systematic review conclusions

The systematic review revealed the paucity of literature on the subject of ICGA in pediatric colorectal surgery. The search ultimately identified 3 articles during which ICGA was employed during a variety of operations including Altemeier procedure, colostomy closure, and most relevant to this thesis, repair of HD and ARM. Overall, no conclusions can be made on the overall effect of ICGA on the development of post-operative anastomotic leak, stricture, and dehiscence. The existing body of literature is

purely observational, reflecting case reports or case series with small patient numbers and no controls. This highlights the need for studies with more rigorous methodology to reduce bias in delineating any advantage of ICGA in pediatric colorectal surgery.

5.4 Feasibility randomized controlled trial conclusions

It is recognized that the ideal way to determine the role of ICGA in repair of HD and ARM is a randomized controlled trial. Considering both HD and ARM are rare conditions, it is imperative to determine if this type of study would be feasible before embarking on a multi-centered trial and investing significant resources. Our protocol was found to achieve a > 80% rate of recruitment of patients and suggests a multicenter RCT may be feasible.

5.5 Future directions

Overall, there is work to be done to reduce the rates of anastomotic leak, stricture and dehiscence among patients who undergo operative repair of HD or ARM. Given promising results in adult literature on the use of ICGA in colorectal surgery, investigating its role in pediatrics is prudent. As it stands, the current literature does not allow any conclusions to be drawn. The next step in investigating the role of ICGA in repair of HD and ARM would be conducting a multi-center randomized controlled trial. The protocol described here was found to be feasible, and should be scaled up with modifications towards this aim.

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Appendices

Appendix 1:STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	19	Retrospective Cohort Study
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	N/A	N/A for thesis, will be present in full manuscript
Introduction				
Background/ratio nale	2	Explain the scientific background and rationale for the investigation being reported	19	Section 2.1 Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	19	We aim to determine the current rate of postoperative stricture and anastomotic leak amongst patients undergoing surgical correction of HD or ARM
Methods				
Study design	4	Present key elements of study design early in the paper	20	Section 2.2. Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	20	Section 2.2 Methods, paragraph 1
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	20-21	Section 2.2 Methods, paragraphs 1 – 3
		<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls		

Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants

(b) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed

Case-control study—For matched studies, give matching criteria and the number of controls per case

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	20-21	Section 2.2 Methods, paragraphs 3 – 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	20-21	Section 2.2 Methods, paragraphs 3 – 7
Bias	9	Describe any efforts to address potential sources of bias	20 - 21	Section 2.2 Methods, dates were chosen to mitigate bias associated with change in operative management Section 2.2 Methods, acknowledgement that study is underpowered to perform multivariate analysis
Study size	10	Explain how the study size was arrived at	20	Section 2.2. Methods, chapter 1, convenience sample given dates available.

Appendix 2: Search Strategy

Web of Science

#3 and #6 and #9 and #12 and English (Languages) and 2011 or 2012 or 2013 or 2014 or 2015 or 2016 or 2017 or 2018 or 2019 or 2020 or 2021 (Publication Years)

11:10 AM

Web of Science Core Collection

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Search

#3 and #6 and #9 and #12

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#10 or #11

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Search

KP=(preterm* or prematur* or postmatur* or perinat* or postnat* or neonat* or newborn* or new-born or infan* or baby* or babies or toddler* or preschool* or child* or pediat* or paediat* or peadiatric* or kid or kids or prepubescen* or prepuberty* or puberty or pubescen* or teen* or young* or youth* or minors* or

under ag* or underag* or juvenil* or girl* or boy* or preadolesc* or adolesc* or nursery school* or prekindergarten or kindergarten* or early childhood education or preschool* or elementary education or elementary school* or primary education or primary school* or K-12* or K12 or 1st-grade* or first-grade* or grade 1 or grade one or 2nd-grade* or second-grade* or grade 2 or grade two or 3rd-grade* or third-grade* or grade 3 or grade three or 4th-grade* or fourth-grade* or grade 4 or grade four or 5th-grade* or fifth-grade* or grade 5 or grade five or 6th-grade* or sixth-grade* or grade 6 or grade six or intermediate general or middle school* or secondary education or secondary school* or 7th-grade* or seventh-grade* or grade 7 or grade seven or 8th-grade* or eight-grade* or grade 8 or grade eight or 9th-grade* or ninth-grade* or grade 9 or grade nine or 10th-grade* or tenth-grade* or grade 10 or grade ten or 11th-grade* or eleventh-grade* or grade 11 or grade eleven or 12th-grade* or twelfth-grade* or grade 12 or grade twelve or junior high* or highschool* or high school*)

11:05 AM

Web of Science Core Collection

1,176,412

Search

TS=(Child or Infant or Adolescent or Minors or Pediatrics or Puberty)

11:03 AM

Web of Science Core Collection

2,676,211

Search

#7 or #8

11:02 AM

Web of Science Core Collection

342,100

Search

KP=(anastomotic leak* or anastomosis or beeding or complication? or h?emorrhag* or stricture?)

11:02 AM

Web of Science Core Collection

179,280

Search

TS=(Intraoperative Complications or Surgical Blood Loss or Postoperative Complications or Postoperative Hemorrhage or Pathologic Constriction or Anastomotic Leak)

11:01 AM

Web of Science Core Collection

205,551

Search

#4 OR #5

10:59 AM

Web of Science Core Collection

1,828,779

Search

KP=(colon* or colorect* or "colonic" or "rectal" or "rectum*" or "Hirschsprung disease" or "anorectal malformation*" or "colorectal surger*")

10:58 AM

Web of Science Core Collection

267,463

Search

TS=(Inflammatory Bowel Diseases or Colitis or Ulcerative Colitis or Hirschsprung Disease or Colonic Neoplasms or Colorectal Neoplasms or Anorectal Malformations or Surgical Anastomosis or Operative Surgical Procedures or Surgery or Colon or Rectum or Colorectal Surgery)

10:56 AM

Web of Science Core Collection

1,676,298

Search

#1 OR #2

10:50 AM

Web of Science Core Collection

38,835

Search

KP=(ix6j1063hv or "3599-32-4 indocyanine green" or "cardio green" or "cardio-green" or "cardiogreen" or "green, indocyanine" or "ix6j1063hv" or "indocyanine green" or "ujoveridin" or "vofaverdin" or "vophaverdin" or "wofaverdin" or "fluorescein angiograph*" or "fluorescence angiograph*" or "fluo-rescent dye?" or "fluorescence imag*" or "indocyanine green fluorescence angiograph*" or "indocyanine green fluorescence imag*" or "ICG" or "ICG-FA" or "ICG-FI")

10:49 AM

Web of Science Core Collection

5,945

Search

TS=(Indocyanine Green OR Coloring Agents OR Fluorescein Angiography OR Fluorescence Angiography)

10:48 AM

Web of Science Core Collection

38,743

OVID MEDLINE

1 Indocyanine Green/ (8553)

2 Coloring Agents/ (47777)

3 Fluorescein Angiography/ (27091)

4 ix6j1063hv.rn. or ("3599-32-4 indocyanine green" or "cardio green" or "cardio-green" or "cardiogreen" or "green, indocyanine" or "ix6j1063hv" or "indocyanine green" or "ujoveridin" or "vofaverdin" or "vophaverdin" or "wofaverdin" or "fluorescein angiograph*" or "fluorescence angiograph*" or "fluo-rescent dye?" or "fluorescence imag*" or "indocyanine green fluorescence angiograph*" or "indocyanine green fluorescence imag*" or "ICG" or "ICG-FA" or "ICG-FI").ti,ab,kw. (39824)

5 or/1-4 (101424)

6 exp Inflammatory Bowel Diseases/su or exp Colitis, Ulcerative/su or Hirschsprung Disease/su or Colonic Neoplasms/su or exp Colorectal Neoplasms/su or Anorectal Malformations/su or Anastomosis, Surgical/ or Surgical Procedures, Operative/ or exp Colon/su or Rectum/su or Colorectal Surgery/ or (colon? or colorect* or "colonic" or "rectal" or "rectum?" or "Hirschsprung disease" or anorectal malformation? or "colorectal surger*").ti,ab,kw. (656750)

7 5 and 6 (2214)

8 Intraoperative Complications/ or Blood Loss, Surgical/ or Postoperative Complications/ or Postoperative Hemorrhage/ or Constriction, Pathologic/ or Anastomotic Leak/ or (anastomotic leak* or anastomosis or beeding or complication? or h?emorrhag* or stricture?).ti,ab,kw. (1553020)

9 7 and 8 (581)

10 exp Child/ or exp Infant/ or Adolescent/ or Minors/ or Pediatrics/ or Puberty/ or (preterm* or prematur* or postmatur* or perinat* or postnat* or neonat* or newborn* or new-born or infan* or baby* or babies or toddler* or preschool* or child* or pediat* or paediat* or peadiatric* or kid or kids or prepubescen* or prepuberty* or puberty or pubescen* or teen* or young* or youth* or minors* or under ag* or underag* or juvenil* or girl* or boy* or preadolesc* or adolesc* or nursery school* or prekindergarten or kindergarten* or early childhood education

or preschool* or elementary education or elementary school* or primary education or primary school* or K-12* or K12 or 1st-grade* or first-grade* or grade 1 or grade one or 2nd-grade* or second-grade* or grade 2 or grade two or 3rd-grade* or third-grade* or grade 3 or grade three or 4th-grade* or fourth-grade* or grade 4 or grade four or 5th-grade* or fifth-grade* or grade 5 or grade five or 6th-grade* or sixth-grade* or grade 6 or grade six or intermediate general or middle school* or secondary education or secondary school* or 7th-grade* or seventh-grade* or grade 7 or grade seven or 8th-grade* or eight-grade* or grade 8 or grade eight or 9th-grade* or ninth-grade* or grade 9 or grade nine or 10th-grade* or tenth-grade* or grade 10 or grade ten or 11th-grade* or eleventh-grade* or grade 11 or grade eleven or 12th-grade* or twelfth-grade* or grade 12 or grade twelve or junior high* or highschool* or high school*).ti,ab,kf. (5202127)

11 9 and 10 (39)

12 exp Animals/ not (exp Animals/ and Humans/) (4885466)

13 11 not 12 (37)

14 limit 13 to (english language and last 10 years) (22)

Embase

1 Indocyanine Green/ (16048)

2 Coloring Agent/ (17200)

3 Fluorescence Angiography/ (23840)

4 ix6j1063hv.rn. or ("3599-32-4 indocyanine green" or "cardio green" or "cardio-green" or "cardiogreen" or "green, indocyanine" or "ix6j1063hv" or "indocyanine green" or "ujoveridin" or "vofaverdin" or "vophaverdin" or "wofaverdin" or "fluorescein angiograph*" or "fluorescence angiograph*" or "fluo-rescent dye?" or "fluorescence imag*" or "indocyanine green fluorescence angiograph*" or "indocyanine green fluorescence imag*" or "ICG" or "ICG-FA" or "ICG-FI").ti,ab,kw. (50711)

5 or/1-4 (82855)

6 exp Inflammatory Bowel Disease/su or Hirschsprung Disease/su or exp Colon Tumor/su or Anorectal Malformation/su or exp Anastomosis/ or Surgery/ or exp Colon/su or exp Rectum/su or Colorectal Surgery/ or (colon? or colorect* or "colonic" or "rectal" or "rectum?" or "Hirschsprung disease" or anorectal malformation? or "colorectal surger*").ti,ab,kw. (1724478)

7 5 and 6 (5778)

8 Peroperative Complication/ or Operative Blood Loss/ or Postoperative Complication/ or Postoperative Hemorrhage/ or "Stenosis, Occlusion and Obstruction"/ or Stenosis/ or Anastomosis Stenosis/ or Colon Stenosis/ or Anastomosis Leakage/ or (anastomotic leak* or anastomosis or beeding or complication? or h?emorrhag* or stricture?).ti,ab,kw. (2195353)

9 7 and 8 (2049)

10 exp Child/ or exp Infant/ or Adolescent/ or "Minor (Person)"/ or Pediatrics/ or Puberty/ or (preterm* or prematur* or postmatur* or perinat* or postnat* or neonat* or newborn* or new-born or infan* or baby* or babies or toddler* or preschool* or child* or pediat* or paediat* or peadiatric* or kid or kids or prepubescen* or prepuberty* or puberty or pubescen* or teen* or young* or youth* or minors* or under ag* or underag* or juvenil* or girl* or boy* or preadolesc* or adolesc* or nursery school* or prekindergarten or kindergarten* or early childhood education or preschool* or elementary education or elementary school* or primary education or primary school* or K-12* or K12 or 1st-grade* or first-grade* or grade 1 or grade one or 2nd-grade* or second-grade* or grade 2 or grade two or 3rd-grade* or third-grade* or grade 3 or grade three or 4th-grade* or fourth-grade* or grade 4 or grade four or 5th-grade* or fifth-grade* or grade 5 or grade five or 6th-grade* or sixth-grade* or grade 6 or grade six or intermediate general or middle school* or secondary education or secondary school* or 7th-grade* or seventh-grade* or grade 7 or grade seven or 8th-grade* or eight-grade* or grade 8 or grade eight or 9th-grade* or ninth-grade* or grade 9 or grade nine or 10th-grade* or tenth-grade* or grade 10 or grade ten or 11th-grade* or eleventh-grade* or grade 11 or grade eleven or 12th-grade* or twelfth-grade* or grade 12 or grade twelve or junior high* or highschool* or high school*).ti,ab,kf. (6114130)

11 9 and 10 (199)

12 exp Animal/ not (exp Animal/ and Human/) (5786519)

13 11 not 12 (193)

14 limit 13 to (english language and last 10 years) (166)

Appendix 3: Clavien-Dindo Classification⁸³

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anesthesia
- IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
- IVa	single organ dysfunction (including dialysis)
- IVb	multiorgan dysfunction
Grade V	Death of a patient

*brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit.

Curriculum Vitae

ACADEMIC BACKGROUND AND TRAINING

General Surgery Resident (2019 - Present) - Schulich School of Medicine, Western University
 MSc in Surgery (2021 – est. Dec 2022) - Schulich School of Medicine, Western University
 Pediatric General Surgery Elective (July 2022) – IWK, Dalhousie University
 Pediatric General Surgery Elective (Aug 2022) – The Hospital for Sick Children, Univ. of Toronto
 Pediatric General Surgery Elective (Oct 2022) – BC Children's Hospital, UBC
 Pediatric General Surgery Elective (Dec 2022) – Alberta Children’s Hospital, University of Calgary
 Doctor of Medicine (2015 - 2019) – Schulich School of Medicine, Western University
 BSc in Microbiology (2011 - 2015) – University of Victoria

AWARDS AND DISTINCTIONS

Pediatric Surgery Research Day at London Health Sciences Center, 2022

- Awarded **best presentation overall**, \$200

Dr. Richard Incelet Award in Thoracic Surgery, 2021

- For resident rotating on service demonstrating **collegiality, professionalism, and compassion**

Canadian Federation of Medical Students - Culture Changer, 2021

- Nominated by medical students recognizing residents who create to a **positive environment**

McLachlin Resident Research Grant, 2020

- To support ongoing research activities, \$2000

Dr. Fred N. Hagerman Memorial Prize in Surgery, 2019

- For one medical student in graduating class showing **greatest merit in surgery**, \$600

Corrine Gehrels Memorial Award, 2018

- Demonstrated **academic achievement, integrity, and compassion**, \$1,500

Schulich Scholarship, 2015-2019

- For demonstrated academic achievement and financial need, \$100,000

RESEARCH PROJECTS

Indocyanine Green Use in Pediatric Colorectal Surgery
 2021-Present. PI: Dr. Andreana Bütter

Role in project: Feasibility randomized controlled trial conception and design, Health Canada approval for use of ICG for this indication, REB creation, patient recruitment, data collection and monitoring, systematic review

Outcomes so far: Presented preliminary data at CAGS Congress 2022, two regional conferences

Projected publications: Anticipated scaling up to multicenter trial, feasibility trial publication once complete, systematic review publication

RESEARCH PROJECTS (continued)

Predictors of Post-Operative Complications Among Pediatric Patients After PSARP or Pull-Through

2021-Present. PI: Dr. Andreana Bütter

Role in project: Retrospective study conception and design, REB creation, chart review, data collection and analysis

Outcomes so far: National study of Hirschsprung Disease complications based on this protocol adopted by the Canadian Consortium for Research in Pediatric Surgery (CanCORPS)

Projected publications: Regional data publication

Reducing revisit to hospital rates among pediatric post-appendectomy patients: A quality improvement project

2020-Present. PI: Dr. Jennifer Lam

Role in project: Assistance in study conception, data collection, abstract creation

Outcomes so far: Presented at CAGS, two regional research conferences

Projected publications: Study publication, ongoing QI initiatives

Predictors of Long-Term Pulmonary Morbidity in Children with Congenital Diaphragmatic Hernia

2017 Summer Student. PI: Dr. Priscilla Chiu

Role in project: Assistance in study conception, data collection, manuscript

Outcomes: Published manuscript in EJPS, presented at EUPSA 2018

The Standardization of Outpatient Procedure (STOP) Narcotics

2017-2020. PI: Dr. Kenneth Leslie

Role in project: Participant identification, data collection and entry

Outcomes: Published manuscript in Annals of Surgical Oncology, presented at ACS

JOURNAL PUBLICATIONS

Wigen, R, Duan, W, Moraes, T, Chiu, P. Predictors of Long-Term Pulmonary Morbidity in Children with Congenital Diaphragmatic Hernia. European Journal of Pediatric Surgery. 2019. DOI: 10.1245/s10434-019-07539-w.

Hartford, L, Van Koughnett, JA, Murphy, P, Knowles, S, **Wigen, R**, Allen, L, Clarke, C,

Brackstone, M, Gray, D, Maciver, A. The Standardization of Outpatient Procedure (STOP) Narcotics: A Prospective Health Systems Intervention to Reduce Opioid Use in Ambulatory Breast Surgery. *Ann Surg Oncol*. 2019. DOI: 10.1245/s10434-019-07539-w.

MANUSCRIPTS IN PROGRESS

Wigen, R, Davidson, J, Vogt, K, Bütter, A. The Use of Indocyanine Green Angiography in Pediatric Colorectal Surgery: A Feasibility Randomized Controlled Trial. (Study ongoing)

Wigen, R, Pitre, E, Davidson, J, Muszynski, L, Dorward, M, Lam, J. Reducing revisit to hospital rates among pediatric post-appendectomy patients: A quality improvement project. (Manuscript in progress)

Wigen, R, Davidson, J, Vogt, K, Bütter, A. Predictors of Post-Operative Complications Among Pediatric Patients After PSARP and Pull-Through: A Retrospective Review. (Manuscript complete)

Wigen, R, Davidson, J, Vogt, K, Bütter, A. The Use of Indocyanine Green Angiography in Pediatric Colorectal Surgery: A Systematic Review. (Manuscript in progress)

ABSTRACTS PRESENTED

Wigen, R, Vogt, K, Seemann, N, Davidson, J, Lam, J, Merritt, N, Bütter, A. The Use of Indocyanine Green Angiography in Pediatric Colorectal Surgery: A Feasibility Randomized Controlled Trial. 53rd Annual Meeting of the Canadian Association of Paediatric Surgeons, 2022.

Wigen, R, Pitre, E, Davidson, J, Muszynski, L, Dorward, M, Lam, J. Reducing revisit to hospital rates among pediatric post-appendectomy patients: A quality improvement project. 53rd Annual Meeting of the Canadian Association of Paediatric Surgeons, 2022.

Wigen, R, Walsler, R, Murphy, P, Van Koughnett, JA, Hilsden, R, Gray, D, Clarke, C, Maciver, A, Parry, N, Leslie, K, Maciver, A. Sustainability of an Opioid Reduction Initiative: One Year Following the Standardization of Outpatient Procedure (STOP) Narcotics Study. ACS Quality and Safety Conference, virtual, 2020.

Wigen, R, Duan, W, Moraes, T, Chiu, P. Predictors of Long-term Pulmonary Morbidity in Children with Congenital Diaphragmatic Hernia (CDH). Oral Presentation. EUPSA Congress, 2018.

Wigen, R, Marinovich, R, Wang, H, Woodcock, N, Jain, A, Qirjazi, E. Improving Control of Mineral Bone Disease in Peritoneal Dialysis Patients. London Health Sciences Day, 2018.

Hartford, L, Murphy, P, Van Koughnett, JA, Hilsden, R, Gray, D, **Wigen, R**, Clarke, C, Maciver, A, Parry, N, Leslie, K, Maciver, A. The Standardization of Outpatient Procedure (STOP)

Narcotics: A Prospective Non-Inferiority Study to Reduce Opioid Use in Outpatient General Surgical Procedures. ACS, 2018.

ACADEMIC ACTIVITIES

Elected Resident Representative on Residency Program Committee, 2019-Present

Elected Resident Representative on Surgical Foundations Committee, 2019-2021

Resident Representative on Canadian Undergraduate Surgical Education Committee, 2020-2022

Women in Surgery Resident Representative, 2022-Ongoing

TEAM Course (Mini-ATLS) Facilitator, 2022

Mentorship of medical students in their pursuit of a career in surgery 2019-Present

PROFESSIONAL MEMBERSHIPS & DEVELOPMENT

Licentiate of the Medical Council of Canada (LMCC) – Awarded January 2022

Canadian Association of General Surgeons Membership – Since 2019

Ontario Association of General Surgeons Membership - Since 2021

ATLS, ACLS – Completed Spring 2019

Surgical Foundations Royal College Examination – Pass, 2020