Intestinal transplantation

Outcome, complications and diagnostic approach

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Cover: Multivisceral graft illustrated by Gustaf Herlenius

Back Cover: Intestinal villi from an endoscopic view illustrated by Alicia Varkey, Gabriel Varkey and Natalie Varkey

All photographs in this thesis were captured by Gustaf Herlenius with prior consent from each patient.

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To the two who gave me life,

The one who set me free,

And my little three.

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ABSTRACT

Background: Intestinal transplantation is a potentially lifesaving procedure conducted in candidates with e.g. intestinal failure. However, a limiting factor has been the complications, which are inherent to the procedure, along with the inadequacies of current modalities to establish a prompt diagnosis of acute cellular rejection. Additionally, most of these procedures are performed in large centres and the outcome in low volume centres is uncertain. The aim of this thesis was to evaluate patients referred for intestinal transplantation in the Nordic countries with emphasis on the procedures and methods to improve surveillance.
Method: Study I & II, patients were assigned to either the waiting list for transplantation or considered unsuitable. Comparisons were made between the groups. The transplanted patients were further highlighted in Study II. In studies III & IV the adequacy of implementing video capsule endoscopy and a new endoscopic scoring system to detect rejection were reviewed.
Results: Survival rate was highest in patients stable on parenteral nutrition in contrast to candidates awaiting transplantation. The 1 & 5 year survival after transplantation was 79 and 65% respectively with rejection in 72% of the patients. Video capsule endoscopy was of clinical benefit in 83% of cases and agreement with histology was moderate ($k=0.54$, $p = 0.05$). The endoscopic scoring system showed a very good inter-rater agreement ($k=0.81$) with an overall sensitivity and specificity of 69 and 83% for rejection and 92 and 86% respectively for severe rejection.
Conclusion: Patient selection was crucial when accepting individuals for intestinal transplantation and the procedure could be lifesaving if chosen adequately. Video capsule endoscopy was useful for detecting complications. The endoscopic score proved efficient on standardizing current practice, but with a risk of missing early signs of rejection and thus insufficient as a singular investigation.
Keywords: Intestinal transplantation, rejection, endoscopy

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SAMMANFATTNING PÅ SVENSKA

Tarmtransplantation är ett ingrepp som definieras av att tunntarmen antingen isolerad eller tillsammans med andra matsmältningsorgan överförs från en givare till en mottagare. Denna operation kan bli nödvändig hos exempelvis personer med en icke-fungerande tarm där den sedvanliga behandlingen med näringsdropp sviktar. Tarmtransplantation utförs sällan och då oftast på större enheter i Europa eller USA, medan resultaten ifrån mindre centra är tvetydig. Anledningar till att antalet transplantationer är begränsade beror delvis på att den medicinska behandlingen oftast fungerar väl och på organbrist, men också på att allvarliga komplikationer såsom avstötning är vanliga och nuvarande metoder för att upptäcka detta är otillräcklig. I denna avhandling var målsättningen att utvärdera patientselektion inför tarmtransplantation i Norden och bedöma vilka patientgrupper som hade en fördelaktig prognos. Fokus läggs därefter på de tarmtransplanterade patienterna med tonvikt på att utvärdera nya metoder för att upptäcka organavstötning. Metoder som utvärderas är kapselendoskopi och ett nytt visuellt graderingsschema vid endoskopi för att upptäcka avstötning. Dessa instrument har inte utvärderats tidigare hos patienter som genomgått tarmtransplantation men kapselendoskopi är en etablerad modalitet för att undersöka patologi i magtarmkanalen.

Våra resultat (studie I & II) visade att patienter som saknade allvarliga komplikationer av parenteral nutrition även hade bäst överlevnad, medan patienter som sattes upp på väntelistan men ej erhöll organ hade en sämre prognos. Ett och femårsöverlevnad efter transplantation var 79 and 65 % med en förekomst av organavstötning bland 72 % av patienterna. Klinisk nytta av kapselendoskopi sågs vid 83 % av undersökningarna med en måttligt bra överensstämmelse med histologi ($k=0.54$, $p = 0.05$). Vidare så visade det endoskopiska graderingsschemat på en mycket bra överenstämmelse mellan bedömare ($k=0.81$) och en sensitivitet och specificitet på 69 och 83 % för avstötning och 92 % och 86 % för svår avstötning.

Sammanfattningsvis så blir vår slutsats att:

- Patientselektion är central för att identifiera vem som har störst nytta av att tarmtransplanteras.
- Överlevnaden bland de nordiska patienterna efter tarmtransplantation motsvarar den internationella erfarenheten.
- Videokapselendoskopi utgör ett värdefullt instrument vid tarmstransplantation.
- Det endoskopiska graderingsschemat är lovande och bör utvärderas prospektivt, men schemat riskerar att missa tidiga tecken på avstötning.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Varkey J, Simrén M, Bosaeus I, Krantz M, Gäbel M, Herlenius G. Survival of patients evaluated for intestinal and multivisceral transplantation - the Scandinavian experience. *Scand J Gastroenterol.* 2013;48(6):702-711.

II. Varkey J, Simrén M, Jalanko H, Oltean M, Saalman R, Gudjonsdottir A, Gäbel M, Borg H, Edenholm M, Bentdal O, Husby S, Staun M, Mäkisalo H, Bosaeus I, Olausson M, Pakarinen M, Herlenius G. Fifteen years' experience of intestinal and multivisceral transplantation in the Nordic countries. *Scand J Gastroenterol.* 2015;50(3):278-290.

III. Varkey J, Oltean M, Pischel AB, Simrén M, Herlenius G. Initial Experience of Video Capsule Endoscopy After Intestinal Transplantation. *Transplant Direct.* 2016;2(12):e119.

IV. Varkey J, Stotzer PO, Simrén M, Herlenius G, Oltean M. The endoscopic surveillance of the transplanted small intestine: a single center experience and a proposal for a grading score. *Scand J Gastroenterol.* 2018;53(2):134-139.

CONTENT

ABBREVIATIONS

ACR	Acute cellular rejection
AI	Artificial intelligence
CMV	Cytomegalovirus
CT	Computed Tomography
EBV	Epstein-Barr virus
GLP-2	Glucagon-like peptide 2
GVHD	Graft-versus host disease
IFALD	Intestinal failure associated liver disease
MRI	Magnetic Resonance Imaging
PN	Parenteral nutrition
PTLD	Post-transplant lymphoproliferative disorder
UNOS	United Network of Organ Sharing

DEFINITIONS IN SHORT

Acute cellular rejection	The consequence of a T-cell mediated immune response of the host against the intestinal graft.
Chronic intestinal failure	Condition characterized by the reduction of bowel function that leads to reduced absorption, resulting in the need of intravenous supplementation to maintain health and/ or growth.
Cohens kappa	A statistical method to measure inter-rater reliability.
Graft-versus host disease	A complication in which the donor´s T-cells recognize the recipient´s system as foreign and activates a response against the recipient, resulting in tissue damage and a systemic reaction.
Intestinal graft	A graft containing the jejuno-ileum.
Multivisceral graft	These grafts include the stomach along with the small intestine and often the liver.
Post-transplant lymphoproliferative disorder	A type of lymphoma in which B-lymphocytes are immortalized, occurring because of a weakened immune system following transplantation.

1 INTRODUCTION

1.1 HISTORICAL ASPECTS OF ORGAN TRANSPLANTATION

The concept of replacing a deceased organ came about in the 1900s. The enthusiasm in realizing this vision was partly due to the technical proficiency of Alex Carrel who developed techniques in suturing blood vessels, making it possible to connect transplanted organs to the host´s vasculature. Carell perfected his skills to such an extent that he foresaw that success in this field was limited by factors other than surgery such as biological compatibility within a species. In 1914 the vascular surgeon Erwin Payr stated that a reduction of the biochemical differences between individuals was the key objective. This realization suggested an intentional suppression of the immune system to achieve improved survival. Unfortunately, these concepts could not be applied clinically, and organ transplantation was consequently given up after World War I. However, the basis of this work established core concepts in transplant medicine as it was revisited in 1945; 1) It is logical to replace a diseased organ to treat a complex disease, 2) In principle, organs are exchangeable (1). Subsequently an American Surgeon, Joseph Murray performed the first successful kidney transplantation in 1954 (2-4).

The following years constituted a grim period in the history of transplantation with heavy mortality and morbidity. Many of the liver and heart transplantation programs that initially started in the 1960s were doomed to close down with only a few liver and heart recipients achieving long-term survival (3). The evidence for organ rejection was further proved by British zoologist Peter Medawar along with plastic surgeon Thomas Gibson during World War II as they developed a rabbit model for studying skin grafting. Their findings were indicative of the immune system being the culprit in the destruction of the skin graft (5). Moreover, Medawar´s group discovered that by injecting cells from one inbred strain of mice to another had a fortunate result in a fraction of the mice who become tolerant to grafts from the strain that donated the tissue (2). The following era improved our understanding of the immune system which resulted in improved development of immunosuppressive drugs.

Similarly, the development of intestinal transplantation has paralleled that of other solid organ transplants and Lillehei in Minnesota performed the first intestinal transplantation in humans in 1967 (6, 7). Seven transplantations were performed by six different teams worldwide until 1970 with a survival that

lasted from 12 hours to 79 days. Unfortunately, these early attempts were hindered by high mortality due to severe rejection and sepsis and it was not until 1988 that the first successful transplantation was performed by Deltz in Kiel, achieving a patient survival of five years. In total, 15 isolated bowel transplants were performed between 1985 and 1990, having used an immunosuppressive protocol based on Cyclosporine. Most of these patients succumbed to early graft rejection and death (7). It was not until the Pittsburgh group (1990-1993) demonstrated the efficacy of Tacrolimus (FK-506) that survival finally began to improve, showing a one-year survival rate of 51-65% for isolated intestines and liver containing grafts (7-9).

The Nordic experience mimics the international experience, revealing a learning curve from the first isolated intestinal transplantation at Uppsala University hospital in 1990 and the Karolinska institute in 1997, where both patients succumbed to death within 9 weeks after the procedure. In 1998, the first multivisceral transplantation was performed by Michael Olausson in Gothenburg, while Gustaf Herlenius conducted the first successful procedure with an isolated intestine in 2007 in Gothenburg (10, 11). Both of these patients achieved long-term survival (>10years), the patient with the multivisceral graft is still alive and well. Intestinal transplantation has progressed from being impossible to a clinical reality, though there still are challenges that need to be addressed.

1.2 GRAFT TYPES

An intestinal transplant is defined as a graft containing the jejuno-ileum. When this portion is transplanted alone, the term isolated intestine is used, but frequently other visceral organs are implanted simultaneously. The rationale for tailor-making each graft depends on several factors: comorbidities in adjacent organs (intestinal pseudo-obstruction), quality of remnant organs (renal failure, chronic pancreatitis), prior surgical removal (gastric bypass, colectomy), extent of disease encapsulating central vascular structures (mesenteric vein thrombosis, desmoid tumours, neuroendocrine pancreatic tumours) and functional and anatomical considerations, such as a reduced domain of the abdominal cavity after previous enterectomy.

The graft therefore consists of either a multivisceral graft with/without the liver (modified multivisceral graft) or organs transplanted separately from one donor. There are three distinct types of intestinal transplantations, but multiple variations of these procedures exist:

- Isolated intestine with/ without colon: This graft is most often utilized in patients with intestinal failure but without advanced liver disease. Liver fibrosis at the time of the procedure is acceptable since these features often regress postoperatively. The inclusion of the ascending colon in candidates without a native colon has shown benefits in graft absorptive function.
- Liver-small intestine: In patients with intestinal failure with end-stage liver disease, this graft type is often preferred.
- Multivisceral transplantation: These grafts include the stomach, pancreaticoduodenal complex along with the small bowel and often the liver. Gastrointestinal tract exenteration is required and the graft is engrafted en bloc. The indications necessitating this procedure are similar to that for liver-small bowel, but also include diffuse porto-mesenteric vein thrombosis, tumours (desmoids, neuro endocrine pancreatic tumours with liver metastases), generalized gastric and intestinal motility diseases, or possibly when re-transplantation may be considered an indication (12-14).

1.3 IMMUNOLOGY

The basis for successful organ transplantation is the acceptance of the donor tissue by the host's immune system, which has the capacity to recognize the tissue as foreign and thereby rejecting it.

Many components of this response (alloimmune response: immune response to non-self) is similar to that of other organ types but the involvement of the small bowel has shown a more vigorous immune response resulting in a higher frequency of allograft rejection. The immunogenicity of the small intestine is derived from many sources since 80% of the immune cells reside in the small intestine. These cells are later repopulated by the recipient's cells but the donor's genotype remains in the epithelium resulting in a chimeric state (tissue containing cells with different genes) and immunogenic graft (14-16). Moreover, the microenvironment of the intestine is predisposed to harmful immune responses, e.g. cross reacting immune responses between pathogens (virus, bacteria) and alloantigens resulting in graft injury (14, 17, 18).

The process is often initiated through the innate immune cells that present the alloantigen to the naïve T-cells, which also could be activated by the effector T-cells. This process may result in the secretion of cytokines (e.g. IL-2) resulting in an inflammatory cascade that could have detrimental effects to the graft. The T-cells may also stimulate the B-cells to produce antibodies, thereby driving humoral mechanisms that could simultaneously injure the graft (19). The presence of donor specific antibodies either at the time of transplantation or thereafter, may have a deleterious effect on graft and patient survival. However, the precise role of these donor specific antibodies needs to be further defined.

As the rejection process has started, the epithelial layers of the intestinal mucosa are now compromised and may lead to a destruction of the mucosal barrier followed by translocation of intraluminal bacteria resulting in sepsis. The occurrence of rejection can develop at any time point after transplantation and may present itself as either cellular rejection or humoral rejection. Additionally, the substantial gut-associated lymphoid tissue that is transferred exposes the host for a significantly increased risk of developing graft-versus host disease (19-21).

1.4 IMMUNOSUPPRESSION

The outcome of organ transplantation is inherently connected to the success and failures in controlling the immune system with immunosuppression. The success in tempering the number of acute cellular rejection episodes has resulted in an increase in the number of transplantations in all organ systems. Despite the efforts in preventing rejection and improving the short term graft survival, long-term results are still lagging behind with minimal changes over the last decades (18, 22, 23). In general, immunosuppressive regimes are therefore not only suboptimal in preventing rejection (acute, chronic) but may also be a risk factor for the development of opportunistic infections, malignancies (particularly post-transplant lymphoproliferative disorder), renal failure as well as metabolic and cardiovascular diseases (24-27). This risk is particularly high in the intestinal transplant recipient where a more intensified immune suppressive protocol is needed, often requiring antibody induction and higher tacrolimus levels (28, 29). Thus, it is important with a thorough monitoring strategy for various complications in addition to a close monitoring of serum levels of the immunosuppressive drugs.

1.5 IMMUNOLOGICAL COMPLICATIONS

The immunological challenges faced by the patient is represented by a chimeric graft comprising of a small intestine that is repopulated by the recipient's cells, while the donor´s genotype remains in the epithelium (15, 16). Although this combination has the potential of creating a wide array of immunological complications, only acute cellular rejection, graft-versus host disease and post-transplant lymphoproliferative disorder will be discussed here.

Acute cellular rejection

Acute cellular rejection (ACR) poses a tough challenge affecting approximately 30-60% of all patients (30). Most (>70%) of these episodes occurred during the first year with a peak around 2-4 weeks post-operatively, but events occurring several years later have also become evident. The duration of each episode varied depending on the severity, ranging from 1 week to about 1 month. Prolonged periods (>21 days) of severe rejection were also associated with graft loss (31). Symptoms such as fever, vomiting, abdominal pain and increased stoma output were indicative of an ongoing process (32). Repeated

episodes of rejections is also believed to predispose for chronic rejection but the pathogenesis of this condition is yet to be established (33).

Post-transplant lymphoproliferative disorder

Post-transplant lymphoproliferative disorder (PTLD) is a term used for lymphoid and plasmacytic proliferations developing after transplantation. Most PTLD have been associated with Epstein-Barr virus (EBV). The pathogenesis is complex and dependent on EBV´s capability in transforming and immortalizing the B lymphocytes. Histopathology should be acquired for diagnostic purposes if a high suspicion is present, but this is not always possible (34). Symptoms associated with the condition include; fever, diarrhoea, weight loss, hypoalbuminemia, palpable mass and/or lymphadenopathy (31).

Graft-versus host disease

Graft-versus host disease (GVHD) is caused by an imbalance of the immune system due to the large quantity of lymphoid content in the graft. Consequently, the donor´s T-cells recognize the recipient´s system as foreign and activates a response against the recipient's antigen presenting cells resulting in tissue damage and a systemic reaction. The diagnosis is made based on clinical findings and confirmed through histopathology from the affected regions (e.g. skin, oral mucosa). Confounders such as viral infections and drug reactions are difficult to differentiate from GVHD and in these cases donor-cell detection might be helpful especially in cases with donor/recipient sex mismatch (35). Clinical findings are most often skin rashes (**Figure 1**), but other manifestations may be present e.g. in the native gut or bone marrow (35-37). Collectively, these conditions have a high prevalence (6-21%) and high mortality (14-78%) (35).

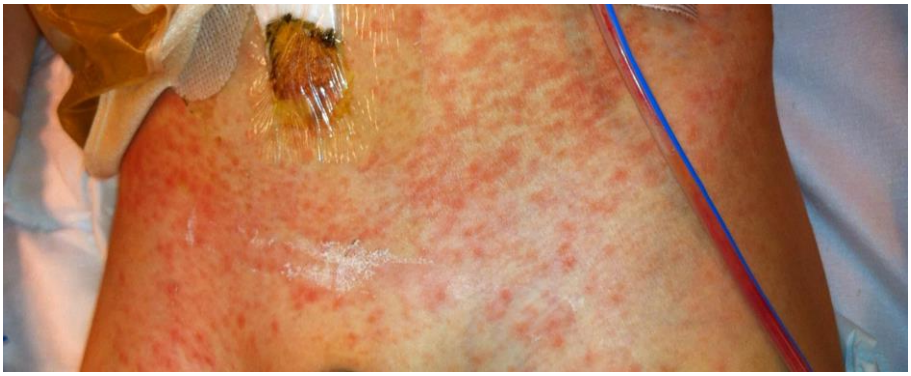

Figure 1. A maculopapular rash caused by GVHD.

1.6 SPECTRUM OF DISEASES

1.6.1 INTESTINAL FAILURE

The classification of intestinal failure can be summarized into three types.

- Type 1: Acute conditions that lasts for a short time and are self-limiting.
- Type 2: Prolonged acute condition requiring parenteral support from weeks to months.
- Type 3: Chronic intestinal failure requiring parenteral support for months to years. This condition may be reversible or irreversible (38, 39).

Chronic intestinal failure is characterized by the reduction of bowel function that leads to a reduced absorption of macronutrients or water and electrolytes, resulting in the need of intravenous supplementation to maintain health and/ or growth (39).

The etiology of the condition varies between adults and children, but can be grouped into the following conditions:

- failure to absorb sufficient nutrition and/or fluid due to a decreased intestinal length i.e. short bowel syndrome (surgical/anatomical disorders).
- conditions bypassing the absorptive surface (fistula).
- diseases resulting in a loss of intestinal function either through restricted intake or inefficient absorptive surface (mucosal disorders, motility diseases) (40).

The treatment of choice for patients with intestinal failure is parenteral nutrition (PN) and before the development of PN these conditions led to certain deaths. Many hurdles did exist prior to the development of a safe PN solution and one major breakthrough was made by Dr. Elman, who demonstrated successful intravenous infusion of amino acids to humans using an enzymatic hydrolysate of casein, and by Arvid Wretlind in 1961, who developed a safe lipid formulation using soybean oil, emulsified by egg yolk phospholipids in glycerols (41). Thereafter, in 1967 reports on the approach on how to place a central venous catheter in the subclavian vein for administration of long-term PN was demonstrated (42). It was now possible to administer long-term PN in

a relative safe manner and that was done in 1967 by Dudrick. He started a girl with intestinal atresia weighing 2kg on PN and the following 22 months resulted in a gradual growth, development and a weight gain of 1.5kg (43). Even though, the treatment is life-sustaining with a remarkable long term survival (64-91% 5 year survival) (44-46), serious complications may arise that can have detrimental consequences including intestinal failure associated liver disease (IFALD), central venous catheter thrombosis and sepsis.

Complications of parenteral nutrition and intestinal failure.

Central venous catheter thrombosis

A central venous catheter constitutes the most important risk for developing thrombosis. Many factors contribute to this process such as compromised blood flow, mechanical injury to the vessel wall, catheter infection, hypercoagulable state and the presence of calcium and dextrose in the PN solutions. Although most thrombi are asymptomatic, serious complications may arise including pulmonary embolism, loss of access, post thrombotic syndrome and an increased risk for developing catheter infections (47). The incidence of catheter thrombosis is estimated to be 0.1-0.2 episodes per 1000 catheter days (48, 49), with a higher proportion observed in the paediatric population (49). Many of these events are subclinical and the actual figures are therefore unknown.

Sepsis

Blood stream infection is the most common reason for death among patients with intestinal failure. The origin of the causal agent may vary from e.g. abdominal cavity, bacterial translocation without perforation, catheter-related bloodstream infections or from other sites such as pneumonia or urinary tract infections. Identifying the site and controlling the infection is therefore of utmost importance (50). A shift in management has also been seen with the aim to salvage an infected catheter whenever possible to preserve long term venous access. In total, central venous catheter tunnelled infections have been reported at a rate of 0.24-0.38 per 1000 catheter days. A high salvage rate has also been demonstrated with a success rate of 55-72% when attempted using antibiotic therapy. The risk for recurrent infection is higher with this strategy (48, 51) and strategies to prevent infections with e.g. the use of taurolidine lock have shown to be effective (52).

Intestinal failure associated liver disease

Intestinal failure associated liver disease (IFALD) is a liver injury that is caused by multiple factors associated with parenteral nutrition and intestinal failure. The diagnosis should be made in the absence of any other parenchymal liver injury, hepatotoxic factors, or biliary obstruction. Unfortunately, no consensus regarding diagnostic criteria exists. However, a combination of clinical, biochemical, radiological and histological findings are recommended by the European Society for Clinical Nutrition and Metabolism (53). Furthermore, a persistent elevation of the alanine transferase, alkaline phosphatase and γ-glutamyl transferase >1.5 upper limit of normal, along with elevated bilirubin is often seen and persists >6months in adults and >6weeks in children with IFALD (54)(50). Similarly, in a point prevalence study, 24% of adult patients had biochemical alterations consistent with this definition (55). A typical feature of IFALD is the presence of cholestasis and steatosis, which may progress to fibrosis and ultimately in end stage liver failure. This disease course is more rapid in infants and has a higher mortality rate in premature infants and babies compared to adults (53). Additionally, ultrashort bowel is an independent risk factor for IFALD in all patients. The importance to determine the presence of early fibrosis before progression to bridging to cirrhosis and portal hypertension (**Figure 2**) is therefore imperative for timely referral for intestinal transplantation (38).

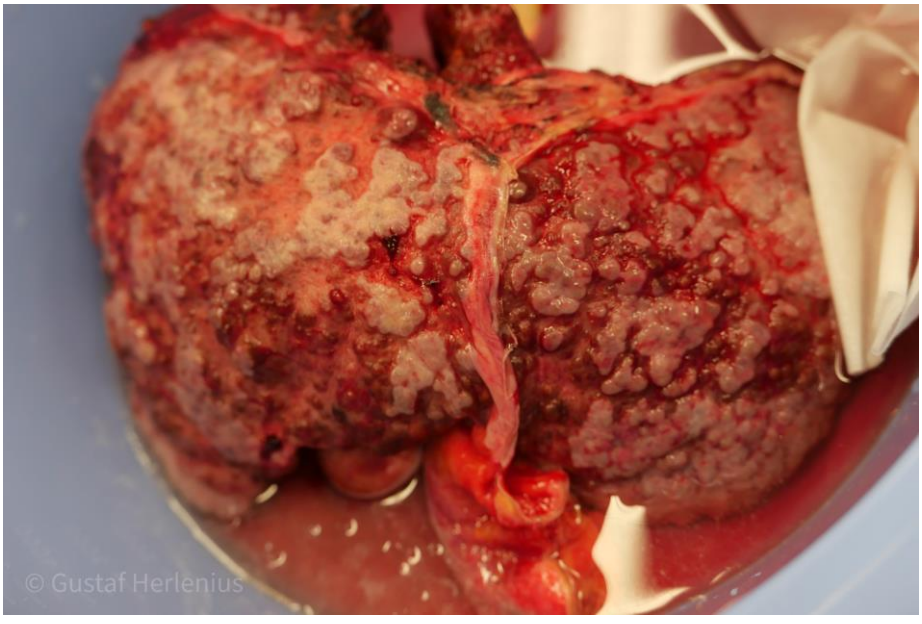

Figure 2. An explanted liver with cirrhosis.

SHORT BOWEL SYNDROME

The length of the small intestine in infants undergoing surgery has been measured to approximately 140cm in the third trimester and 300cm at term (56). In adults, these measurements have been approximately 500cm (ranging between 280-840cm) from the ligament of Treitz depending on the height and sex of the individual (57, 58), 40% of this length consists of jejunum and 60% of ileum. Moreover, the duodenum has been measured to 25-30cm (59)

Short bowel syndrome is a condition resulting from extensive resection resulting in a small bowel length of less than 150-200cm in adults (60). Consequently, 75cm of the remnant small bowel was seen as a negative indicator for survival in infants. The presence of an ileocecal valve, intestinal continuity and an intact colon improved the adaptation and survival (61, 62). In short, the three distinct types of bowel circuits are:

- end-jejunostomy (jejunum is anastomosed directly to the skin).
- jejunocolic (jejunum is joined to a portion of the colon or to the colon in its entirety).
- jejunoileal anastomosis (parts of the jejunum and ileum remains as well as the ileocecal valve and the colon).

The length of the small bowel differentiated patients with transient from chronic intestinal failure. Cut-off values of small bowel length predictive of achieving nutritional autonomy was >100cm in end-jejunostomy, >65cm in jejunocolic and >30 cm in the jejunoileal anastomosis respectively (63).

Etiology of short bowel syndrome

Short bowel syndrome is the most common cause for intestinal failure representing almost 80% of the adult patients and 50% of the paediatric cohort on long-term parenteral support. The most prevalent reasons for extensive resection in the adult population were mesenteric infarction (arterial or venous ischaemia) (36%), Crohn´s disease (29%), and radiation enteritis (10%), followed by surgical complications in 8%. In the paediatric cohort, most children had intestinal malformations (48%), followed by volvulus (25%) and necrotizing enterocolitis (15%) (64).

Management

Adequate management of the primary diagnosis is the key for prevention of massive resection and the development of short bowel syndrome.

For example, acute mesenteric ischemia is the most common cause for short bowel syndrome and is a result of a decreased blood flow due to embolism, thrombosis, or a state with a continuous low splanchnic blood flow. An early diagnosis of this condition and adequate intervention is therefore essential to prevent necrosis and massive resections (60). After resection, independent of the etiology, a gradual adaptation of the bowel occurs, and absorption improves. The more limited the absorptive capacity, the slower the recovery. Furthermore, medical therapy with Glucagon-like peptide 2 (GLP-2) has shown to be promising in both adult and paediatric patients to improve intestinal adaptation and the weaning of PN (65, 66). The possibility to administer these drugs are however limited to a few countries due to financial reasons. Surgical procedures are nonetheless important. In all patients with an enterostomy, the possibility to restore the gastrointestinal tract should be considered, especially by including the colon whenever possible. These interventions may improve the adaptation (67). In children with insufficient bowel length, techniques to increase the intestinal contact area have also been described (longitudinal intestinal lengthening and tailoring, serial transverse enteroplasty) with intriguing results (68). Unfortunately, these techniques are more difficult to implement in the adult patients (67)

DYSMOTILITY

Motility disorders have been classified as either congenital or acquired, depending on the onset of the disease. Here we will focus on motility disorders where intestinal failure is frequent and intestinal transplantation may be considered i.e. chronic intestinal pseudo-obstruction and Hirshsprung´s disease.

Chronic intestinal pseudo-obstruction is a condition characterized by impaired intestinal motility resulting in a decreased propulsion of gut content in the absence of an obstruction. The condition is classified as either primary (no etiopathogenetic cause identified), secondary (e.g. neurological disorders, drugs) or familial (69). Furthermore, sub-classification based on disease location can be made, i.e. if the damage is localized in the enteric nervous system (neuropathy), smooth muscles (myopathy), and /or the interstitial cells of Cajal (mesenchymopathy) (70). This condition affects both adults and children, and approximately 20-50% of the adults and >80% of the children will develop the need for PN (71).

Hirschsprung´s disease is a congenital condition with absence of nerve cells (ganglion) in a segment of the bowel. The length of the affected segment varies from the distal colon to a total colonic and small bowel aganglionosis (72).Total colonic and small bowel aganglionosis is the most rare subtype of Hirschsprung´s disease and leads to extensive resection with sometimes residual bowel lengths shorter than 20cm (73). Prior to the era of intestinal transplantation multiple non-transplant surgical techniques were developed, although with limited benefits (74, 75).

MUCOSAL DISEASE

Congenital enterocyte disorders are inherited conditions with onset early in life. These disorders are characterized by typical histological and structural features resulting in an impaired epithelium of the gut with subsequent loss of absorptive capacity, this often necessitates the need for PN or intestinal transplantation. The main conditions that are included in this group are microvillus inclusion disease, congenital tufting enteropathy and phenotypic diarrhoea (76). The natural history of each disease is also known to differ. For example patients with congenital tufting enteropathy have been found to have an increased potential of weaning off PN with increasing age, and a majority having enteral autonomy by early adult life (77). Therefore, if possible, patients with congenital tufting enteropathy should not undergo intestinal transplantation. On the contrary, similar remissions have not been observed in patients with microvillus inclusion disease. Instead, worsening of the condition has been observed with an increased risk to develop liver failure and a shortened life span (78, 79).

For the adult population on PN, mucosal diseases are either acquired or congenital and consists primarily of e.g. paediatric patients transferring to adult care, coeliac disease, Crohn´s disease, lymphangiectasis, immunodeficiency syndrome and radiation enteritis (64).

1.6.2 MESENTERIC ISCHEMIA

Mesenteric ischemia is a condition that results in a decreased mesenteric blood flow. It may originate from arterial occlusion, venous occlusion, or non-occlusive mesenteric ischemia. Most often the cause is arterial obstruction which is further subdivided into an acute or a chronic presentation (80). Acute ischemia is most often caused by embolic occlusion, which is seen in 50% of the cases, followed by thrombosis of a previously stenotic vessel in 20-30% (81, 82). These conditions may result in severe ischemia and necrosis without intervention since more time is required for the collateral network of the mesenteric circulation to compensate for the decrease in blood flow (80). Similarly, during the advent of acute abdominal trauma, mesenteric vessels may be subjected to injury. The consequence of this damage may be life-threatening or result in debilitating conditions such as intestinal failure due to extensive resection. Additionally, these patients are at a risk of developing

fistulations e.g. high-output intestinal fistulae, pancreatic and biliary fistulae as well as blind loops (83-85).

Mesenteric venous thrombosis represent 5-15% of all patients that have mesenteric ischemia, of these cases approximately 2% are of an advanced nature and classified as diffuse portomesenteric venous thrombosis or complex portomesenteric venous thrombosis (86). The condition is often caused by thrombophilia, trauma, malignancy or inflammation in the biliary system (82, 87). Moreover, the development of portal vein thrombosis is common among patients with liver cirrhosis ranging from 0.6 to 26% and may further complicate the technique used for liver transplantation (88-90). The grade of the thrombus prior to liver transplantation will further guide the clinician to appropriate medical and surgical techniques (91).

The surgical reconstruction during liver transplantation may result in either a portal flow which is physiologic or non-physiological. Physiologic circulation occurs when the splanchnic blood flow passes through the liver either from a porto-portal anastomosis or from a large portosystemic shunt (spontaneous, surgical) connected to the liver graft. This differentiation is important since the inability to recreate a physiologic portal flow will result in a maintained portal hypertension (86). Multivisceral transplantation should be considered as one of the main treatment strategies in this scenario (86, 92).

1.6.3 DESMOID TUMOURS

Desmoid fibromatosis are rare tumours consisting of myofibroblasts. The tumours are caused primarily by mutations in either the b-catenin, resulting in the sporadic rise of tumours, or the genes coding for the adenomatous polyposis coli protein which is associated with the familial polyposis syndrome (93). These tumours are considered "benign malignancies" since they will not metastasize, but may have a fast growth causing local invasion and potentially involving major blood vessels, resulting in the need for major bowel resections or even multivisceral transplantation (94). The disease location is often in the abdominal wall and within the mesentery, but they may appear anywhere in the body and can have a high recurrence rate.

The natural history of desmoids are difficult to predict and depends on the tumour biology, location, and the surgical morbidity of the procedure. There are some tumours regressing spontaneously without any treatment, while others require a more aggressive approach (extensive surgery, radiation, systemic therapies) (95).

1.6.4 NEUROENDOCRINE PANCREATIC TUMOURS

Neuroendocrine tumours are characterized by the presence of neurosecretory granules along with similar histological and immunological profiles. The tumours may arise at different sites but share resemblance in morphology and expression of proteins depending on the stage of differentiation. Variations exists in different anatomical regions with alterations in expression of hormones and transcription factors. Furthermore, grading of pancreatic lesions has shown to have a prognostic value and is based on mitotic count and ki-67 (an antigen displayed only in the nuclei of cycling cells) index. Differentiation from one type to another may occur either in the primary tumour or at a metastatic site (96). One of the most prevalent sites for metastasis is the liver, which affects 28-77% of all patients (97) (**Figure 3**). The optimal management of these lesions is currently debated, but includes non-surgical treatment options such as chemotherapy, immunotherapy, octreotide, lantride and ablative techniques as well as surgical techniques focusing on resection, debulking strategies and in selected cases liver transplantation or multivisceral

transplantation. However, the recurrence rate is high after transplantation and a worsened prognosis has been observed in cases with a high tumour burden and a high ki-67 (98).

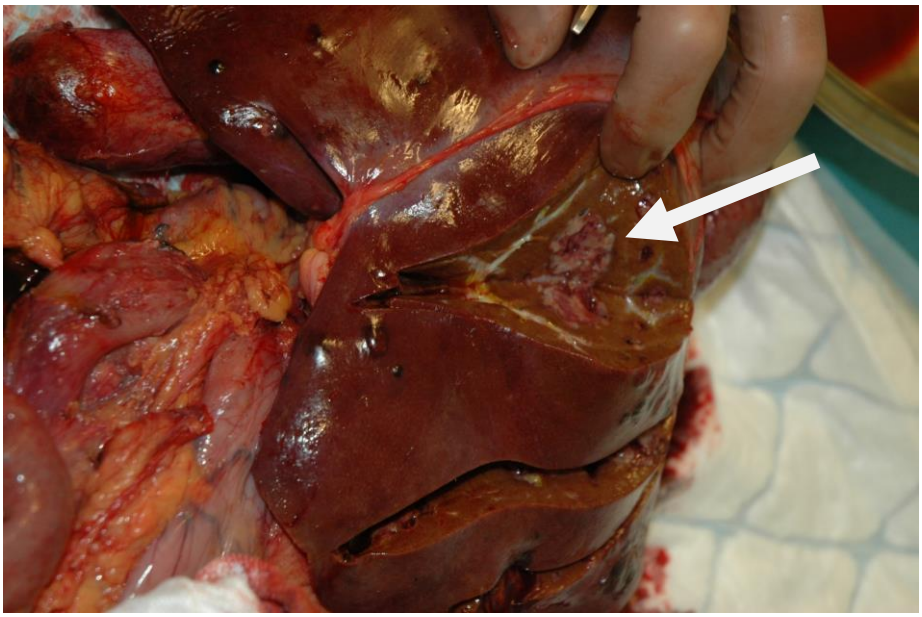

Figure 3. An explanted liver with metastasis (arrow) from a neuroendocrine pancreatic tumour.

1.7 INDICATIONS FOR TRANSPLANTATION

The indications for intestinal transplantation have since the publication in 2001 undergone modifications (99). Intestinal failure with life-threatening complications has constituted the bulk of the patient load. However, as multidisciplinary management has increasingly been implemented within the framework of intestinal failure units, many complications have shown to have a significant degree of reversibility, particularly in patients with short bowel syndrome. For this reason, a working group from the International Small Bowel Transplant Symposium was formed in 2015, and new recommendations were published in 2020. These recommendations continue to highlight the importance of early referral, which enable better recognition of scenarios contributing to adverse outcomes e.g. liver disease, venous thrombosis (>2/4 upper body central venous thrombosis), ultra-short bowel (<10cm in children and 20cm in adults), microvillous inclusion disease and frozen abdomen. These patients may not need a graft immediately but are in risk of deteriorating and should therefore have a close follow-up. Criteria for listing for intestinal transplantation, under the condition that other rehabilitation options have previously been explored, are the following:

1) Advanced or progressive IFALD (Bilirubin >75 μmol/L), portal hypertension.
2) Thrombosis of 3 of 4 upper body central veins or the occlusion of a brachiocephalic vein in children.
3) Life threatening morbidity in children with 2 admissions to the intensive care unit because of cardiorespiratory failure (mechanical ventilation or inotropes) caused by intestinal failure related complications.
4) Invasive intra-abdominal desmoids.
5) Acute intestinal infarction with hepatic failure.
6) Retransplantation due to graft failure (100).

Moreover, a trend has been observed with expanding indications for patients with dysmotility, advanced portomesenteric thrombosis and intra-abdominal tumours (predominantly desmoid tumours) (92, 101-104). However, these recommendations are based on the cumulative international experience consisting primarily of the experience of a few large volume centres. The importance of adapting these strategies to the Nordic cohort is necessary, considering the risk/benefit ratio of each available approach. Most often transplantation is considered only after other treatment regimens have failed or considered unfeasible, as a last resort to save the patient's life.

1.8 ALLOGRAFT MONITORING FOR ACR

1.8.1 ENDOSCOPIC SURVEILLANCE

Endoscopy with intestinal mucosal biopsies is the mainstay for graft surveillance and the golden standard for diagnosing ACR. Therefore, centres have a rigorous surveillance protocol to enable detection of ACR. The corresponding treatment is subsequently based on the clinical situation along with both the endoscopic and histological findings. Unfortunately, the community is deprived of a universal endoscopic grading system for ACR, which would have aided in both diagnosing ACR and grading of the findings. Surveillance strategies vary between centres, but most programs perform weekly investigations for 1-3 months, followed by a bi-monthly plan for the next 3-6 months and thereafter annually. The procedure is often undertaken with ileoscopies/colonoscopies for surveillance purposes, along with gastroscopy if the patient is symptomatic, although, some centres perform both upper and lower endoscopy as part of their surveillance routine (33, 105). The endoscopic characteristics of ACR have been described and include non-specific findings such as erythema, friability, granularity or ulcerations (106) (**Figure 4**). Other conditions displaying specific features on imaging include viral enteritis e.g. cytomegalovirus (CMV), adenovirus. Gastrointestinal CMV infection presents with multiple shallow ulcers and erosions with otherwise normal mucosa, which contrasts with the adenovirus infection that only rarely leads to ulcerations. Specific staining techniques can help to identify these viral infections. To further improve the differentiation between virus and ACR, biopsies from both the graft and the native bowel may be helpful (33, 107).

1.8.2 HISTOPATHOLOGY

The findings consistent with ACR include histologic features of architectorial distortion, inflammation in the lamina propria, epithelial injury, crypt apoptosis and ulcerations (108). These findings are not pathognomonic for ACR, but some of these attributes can be mimicked by other etiologies e.g. viral enteritis (CMV, adenovirus), clostridium difficile infection or drug reactions (mycophenolate mofetil). Clues to identify the causative agent can sometimes be found by investigating similar features in the native gut or if virus inclusion bodies are present (109, 110).

1.8.3 BIOMARKERS

Multiple biomarkers have been tested in the setting of ACR. A common shortcoming for all tests includes the inability to differentiate ACR from other causes of inflammation, e.g. infectious enteritis. Therefore, these tests can at best be considered to be screening tools for excluding an ongoing process in asymptomatic patients. The markers that are best studied for this indication are citrulline and calprotectin. Citrulline, is an amino acid derived from the enterocytes, reflecting the functional mass of the intestine and has therefore been suggested to be a valid biomarker for ACR. However, many factors such as renal function, infection and the natural course after the procedure all complicate the interpretation of these results. When summarizing existing results, citrulline seems to be useful for excluding advanced ACR, but not ACR in its earlier stages (111). Calprotectin, a protein found in the neutrophils, seems to have high sensitivity but low specificity for detection of ACR, thus illustrating its potential as a screening tool but also its limitation in diagnosing ACR (112, 113). The need to improve our diagnostic modalities and standardize the management of intestinal transplant patients is therefore essential.

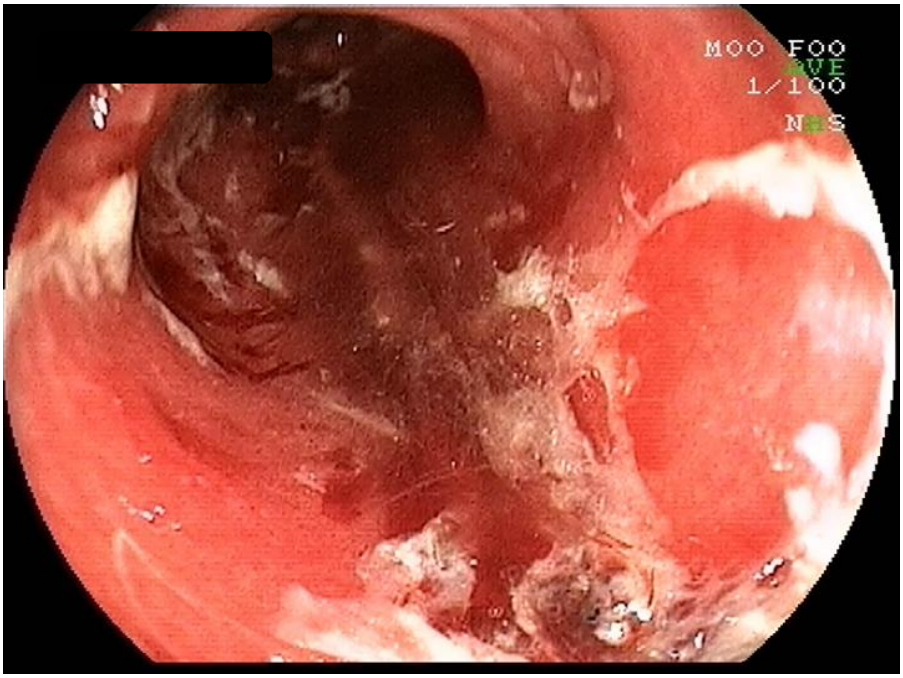

Figure 4. An endoscopic image of the small bowel, where the mucosal layer is completely absent due to exfoliative ACR.

2 AIM

The main aims and data collection for the four studies are summarized in **Figure 5**. The patient cohorts used in the different studies overlap, which is illustrated in **Figure 6** and **Figure 7**. Studies 1 and 2 describe outcome measures in patients who have been referred for intestinal transplantation or have undergone intestinal transplantation. Papers 3&4 focus on evaluating endoscopic modalities that may detect immunological complications with emphasis on ACR. In summary, the aim of this thesis was to evaluate the Nordic patients referred for intestinal transplantation with emphasis on transplant procedures and methods to improve surveillance. The colour coding used in **Figure 5** indicates a specific paper and will be consistent throughout the thesis. Paper 1-4 will be abbreviated to I, II, III, IV.

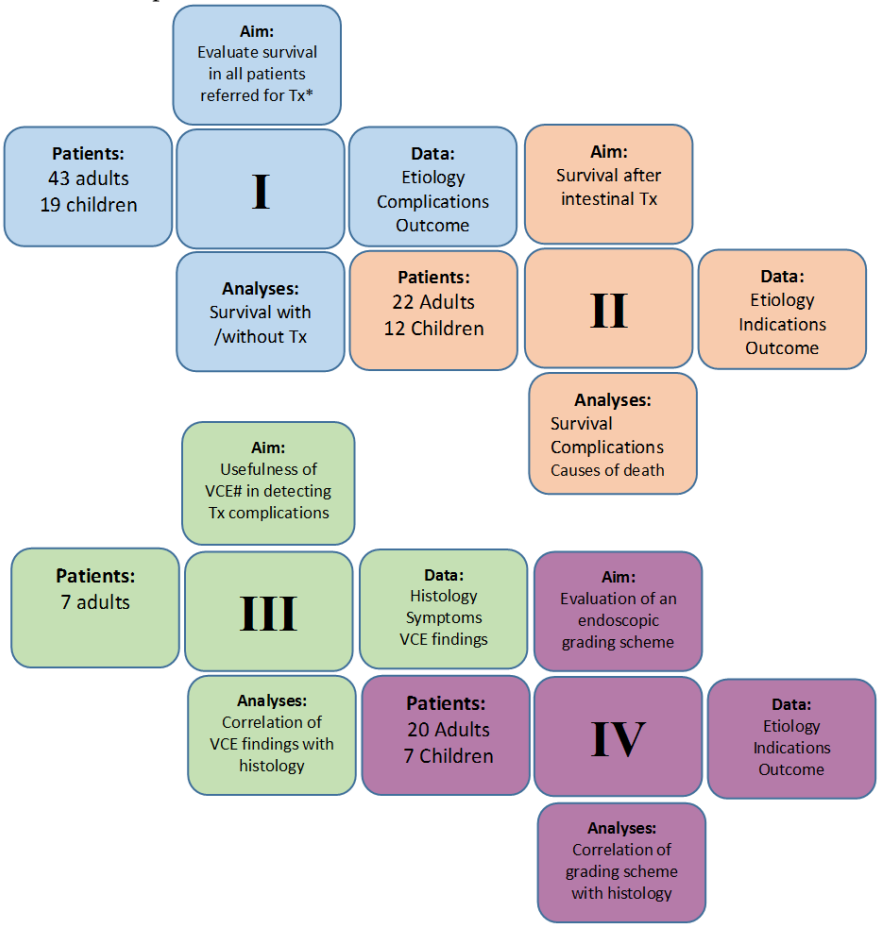

*Figure 5. Overview of aims and methods in paper I- IV. *Transplantation (Tx), # Video capsule endoscopy (VCE)*

3 PATIENTS AND METHODS

3.1 PATIENTS

The patients in these studies were primarily included from the Sahlgrenska University hospital, Gothenburg, Sweden for adult patients, and the Queen Silvia Children´s hospital, Gothenburg, Sweden for paediatric patients, during the time period 1998 to 2016. The Sahlgrenska University hospital and the Queen Silvia Children´s hospital are national centres for intestinal transplantation, and transplantations for both Sweden and Norway are performed here. The second paper (II) additionally included a cohort of Nordic patients that underwent transplantation in either Finland or countries outside the Nordic region. The adult and paediatric cohorts transplanted within Gothenburg (Sahlgrenska University hospital and the Queen Silvia Children´s hospital) consisted of patients that were referred from regions covering the entirety of Sweden and Norway. The following figure (**Figure 6**) illustrates the cohorts that were included in each study. The transplanted patients are further highlighted in **Figure 7**, illustrating the overlap of patients between the studies. Characteristics of each cohort are described in **Table 1.**

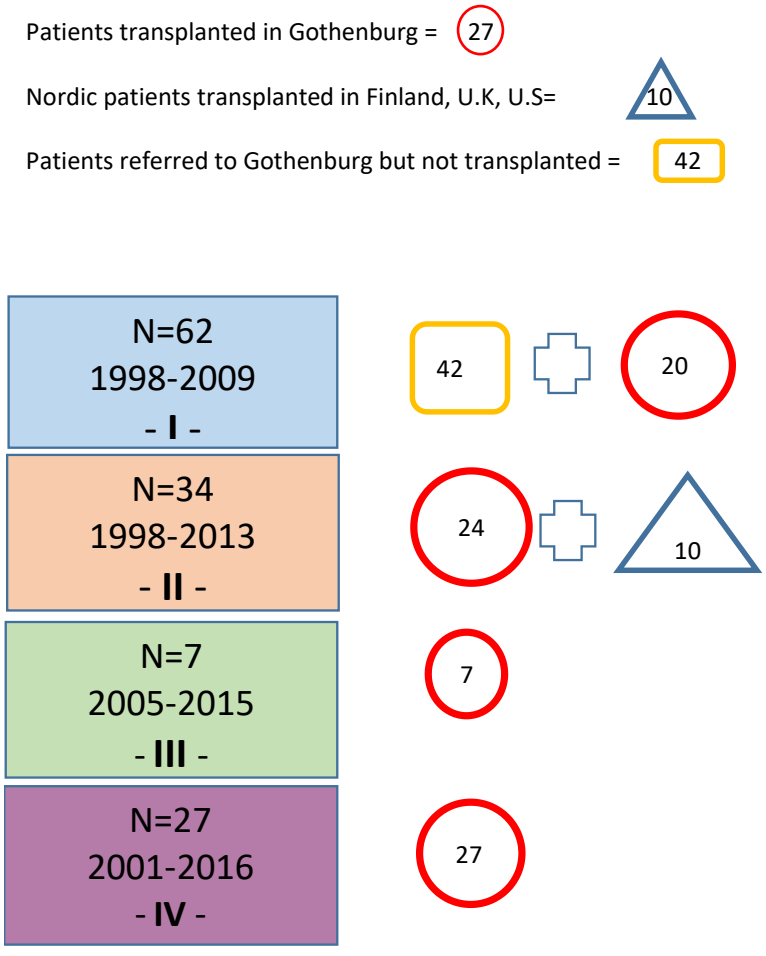

Figure 6. Each study consisted of overlapping time periods within the study period of 1998- 2016. The study period for each paper indicates when a certain examination/review was performed but does not refer to when a specific patient underwent transplantation. Therefore, each patient may or may not have undergone a transplantation prior to the given study period.

Overlap of patients that underwent intestinal transplantation in Gothenburg

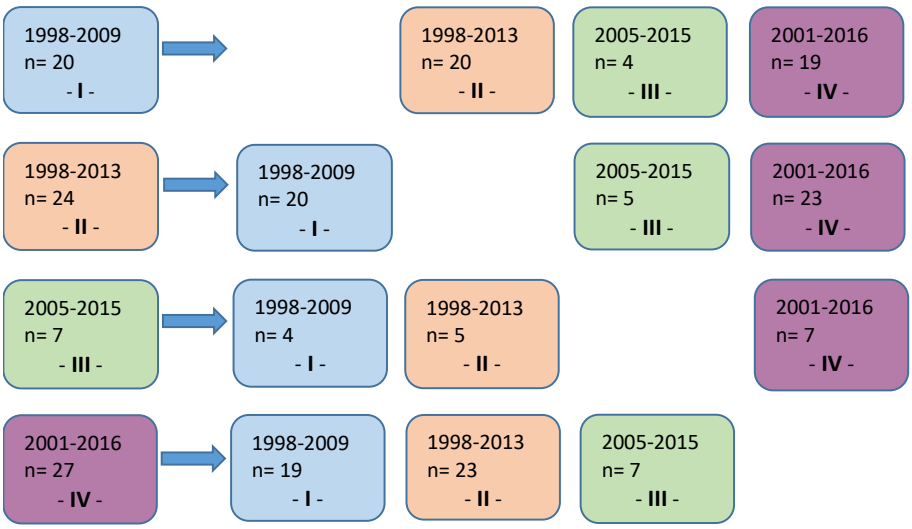

Figure 7. The overlap between cohorts in the studies. All patients that were referred to Gothenburg in the given time period were subsequently included in paper I; all transplanted patients in the Nordic region were included in study II; and every transplanted patient who underwent either a video capsule endoscopy or an ileoscopy in Gothenburg were included in paper III and IV, respectively.

Characteristics of the patients included in study I, II, III, IV are shown in **Table 1**. The numbers included reflect patients that were referred for transplantation but did not receive a graft, all patients transplanted in Gothenburg, and patients that were either transplanted in Finland or outside the Nordic region. All the studies were approved by the Swedish Regional Ethical Review Board at the University of Gothenburg (Study I, II, III DNR 319-11 and Study IV DNR 263-13)

	Referred for Tx 98-09*		**Tx Gothenburg 98-16**		Tx Finland/abroad 98-13	
	Adults	Children	**Adults**	**Children**	Adults	Children
No of patients	28	14	**22**	**8**	5	5
Female	18 (64%)	7 (50%)	**14 (64%)**	**6 (75%)**	1 (20%)	4 (80%)
Age	48(20-67)	7 (0.5-17)	**43(21-67)**	**7(4-17)**	44(31-53)	6(4-17)
Etiology						
Neoplastic disorders	6 (21%)		**6 (27%)**	**1 (13%)**	1 (20%)	
Short bowel syndrome	11 (39%)	2 (14%)	**7 (32%)**	**1 (13%)**		
Dysmotility	6 (21%)	4 (29%)	**5 (23%)**	**3 (37%)**	2 (40%)	5 (100%)
Mesenteric ischemia	3 (11%)	1 (7%)	**4 (18%)**		1 (20%)	
Other causes	2 (8%)	7 (50%)		**3 (37%)**	1 (20%)	
Type of graft						
Isolated small intestine			**2 (9%)**	**3 (38%)**	3 (60%)	4 (80%)
Liver containing			**20 (91%)**	**5 (62%)**	2 (40%)	1 (20%)

Table 1. Patient characteristics for all patients included in study I-IV. *The cohort *"referred for intestinal transplantation but not transplanted" is included in paper* I, *and the patients transplanted outside of Gothenburg is included in paper* II. *The middle column, "Transplanted patients in Gothenburg", include all patients that were transplanted in Gothenburg during the course of this thesis (paper* I-IV*). The differences in study periods determined the eligibility of a patient for a particular study.*

3.2 METHODS

All studies focus on different aspects of patient management and outcome. This figure (**Figure 8**) illustrates the main objectives being addressed in each study and shows how all projects are interlinked.

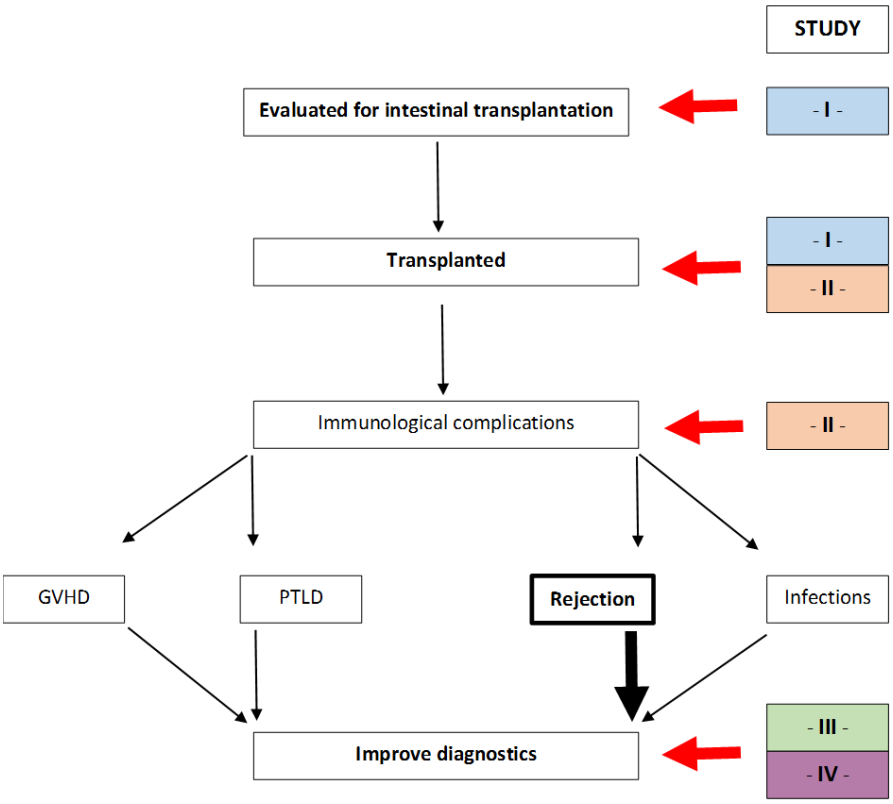

Figure 8. A summary of the study objective for paper I-IV.

3.2.1 SUMMARY OF STUDY DESIGN PAPER I AND II

These retrospective studies included all patients that were referred for intestinal transplantation and Nordic patients that either underwent transplantation inside or outside the Nordic region. The cohort included both children and adults with various indications and etiologies. Patients were further stratified to either the transplant waiting list or deemed unsuitable for transplantation. Reasons for declining a candidate varied from being stable on PN to patients that had direct contraindications. Thereafter, comparisons were made between each of these groups and the reasons for demise were analysed. The patients that underwent intestinal transplantation were further highlighted in the Nordic survey with focus on describing the cohort with regards to indications for transplantation, graft selection and the presence of immunological complications such as ACR, PTLD and GVHD.

3.2.1 SUMMARY OF STUDY DESIGN PAPER III AND IV

Both of these studies were derived from a retrospective material and based on the transplanted cohort from Gothenburg alone. The reasons for undergoing either video capsule endoscopy or ileoscopy were to detect immunological complications or for surveillance purposes. The focus was to analyse new methods to detect ACR, using an instrument that had not previously been analysed and to evaluate its usefulness. Whenever feasible, comparison with the golden standard, i.e. histology, was done.

Study III: In total, 12 video capsule endoscopies were performed in seven patients using three different video capsules with similar features (EndoCapsule, Pillcam SB, Microcam). The procedures were performed following a clear liquid diet and ingestion of two litres of polyethylene glycol solution on the day prior to the examination. The usefulness of video capsule endoscopy and the risks attributed to the procedure were evaluated.

Study IV: An endoscopic grading score for ACR was constructed and each of the reports from the 512 ileoscopies were reviewed by two investigators and graded accordingly. The agreement between the reviewers were evaluated, followed by a consensus agreement when the scores differed. The consensus scores were thereafter compared with the histologic findings. False positive results included mucosal findings in the absence of histologic features and false negative results included normal endoscopies in the presence of histologic findings. The review was blinded with regards to the clinical course and histology. Faecal calprotectin and endoscopy systems with high definition were also used in a portion of the patients, and the impact of these factors were analysed separately.

3.2.2 INDICATIONS FOR TRANSPLANTATION (STUDY I & II)

The criteria required for accepting patients with intestinal failure to undergo intestinal transplantation were primarily based on the presence of severe complications as defined by the American Gastroenterological Association guidelines such as IFALD, thrombosis, or frequent episodes of septicaemia (99, 114). In exceptional cases, a severely reduced quality of life among patients with intestinal pseudo-obstruction was considered an acceptable indication.

Mesenteric ischemia, due to either arterial occlusion/rupture or mesenteric vein thrombosis was another indication that was utilized. For patients with complex portomesenteric vein thrombosis, intestinal failure was not a prerequisite but of concern to resolve life-threatening complications of portal hypertension, unless other treatment strategies were considered and reckoned unfeasible.

Neoplastic conditions such as neuroendocrine pancreatic tumours or desmoid tumours are also recognised indications, especially when the tumour is unresectable by conventional surgical techniques due to infiltration of the mesenteric root (115, 116). Furthermore, a short habitual life-expectancy and an absence of extrahepatic spread were expected in patients listed with neuroendocrine pancreatic tumours.

In certain patients transplant procedures are contraindicated and these factors are similar to all solid organ transplantations. Absolute contraindications consist of multi-organ failure, severe infection, and malignancy beyond accepted oncological criteria. Relative factors include severe sarcopenia or admission to the intensive care unit at the time of the evaluation. Factors such as psychiatric illness, less than two patent vascular accesses, social and compliance issues, were also considered to be contraindications.

3.2.3 GRAFT SELECTION (STUDY II)

Grafts were obtained from deceased donors and the composition of each graft depended on the individual needs of each patient. The match between donors and recipients were primarily based on the blood type and body weight ratio. Factors contributing to the choice of graft consisted of multiple factors e.g. the presence of liver disease, portal hypertension, underlying etiology and the preference of each given centre. The stratification of procedures was simplified into two main transplantation categories **(Figure 9),** although multiple variations of these grafts exist.

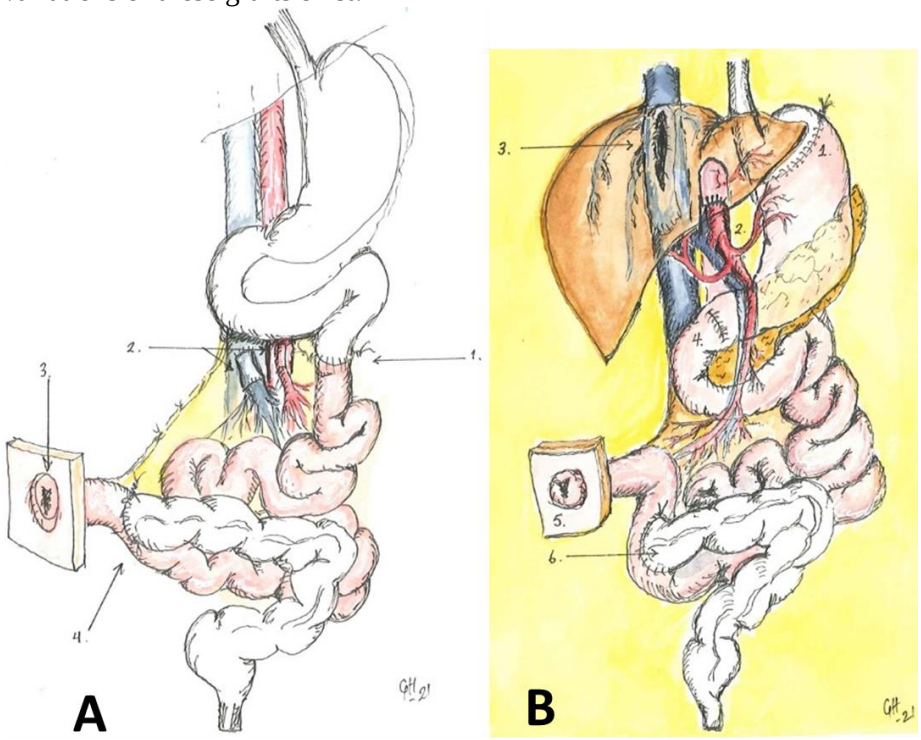

Figure 9. The two main types of grafts used. ***A****: Isolated intestinal graft; 1. Proximal gastrointestinal anastomosis, 2. Vascular anastomoses, 3. Graft ileostoma, 4. Distal gastrointestinal anastomosis.* ***B****: Multivisceral graft; 1. proximal gastrointestinal anastomosis, 2. Aortic conduit, 3. Cavo-caval anastomosis, 4. Pyloroplasty, 5. Graft ileostoma, 6. Distal gastrointestinal anastomosis. Illustrations courtesy of Gustaf Herlenius.*

Isolated intestinal graft was used for patients with intestinal failure who did not yet have liver disease or complicated portal hypertension. Liver containing allografts were primarily used in candidates with intestinal failure and advanced IFALD, in patients who succumbed to mesenteric ischemia and in selected cases with desmoid tumours, severe dysmotility and neuroendocrine pancreatic tumours

3.2.4 IMMUNOLOGICAL COMPLICATIONS (STUDY II)

Immunological complications were common, and these studies primarily focused on ACR, PTLD and GVHD. The definitions used in our studies are described below.

An episode of ACR was defined based on histology and if the patient had received antirejection treatment with either corticosteroids or monoclonal antibodies (anti-thymocyte globulin, muronab CD3, rituximab). The histologic grading of ACR was based on the features described by Wu et. al (108). Each set of biopsies were further graded as indeterminate, mild, moderate, or severe rejection, depending on the presence of infiltration of primarily mononuclear inflammatory cells, crypt injury and increased apoptotic bodies.

PTLD was diagnosed using quantitative EBV DNA PCR assay and imaging [Computed Tomography (CT), Magnetic Resonance Imaging (MRI), positron emission tomography scans] along with histopathological confirmation of PTLD from the lesion and lymph nodes.

The diagnosis of GVHD was confirmed if clinical findings, histology, and preferably chimerism in peripheral blood were consistent with the diagnosis. Passenger leukocyte syndrome was included in this group and was diagnosed if the patient had haemolysis due to donor-derived antibodies.

3.2.5 VIDEO CAPSULE ENDOSCOPY (STUDY III)

The indications for performing a video capsule endoscopy was to answer a clinical query that other standardized methods failed to answer. Investigations such as CT scans, stool cultures, viral screens and upper and lower endoscopy had already been performed but deemed insufficient in these cases. Furthermore, common symptoms in this cohort consisted of abdominal pain and high stoma output, which in certain instances may have been associated with a more severe etiology and therefore supporting the usefulness of capsule endoscopy. Since only a short segment of the intestine is covered using conventional endoscopy, the potential presence of ACR in other intestinal segments was also a reason for using capsule endoscopy, especially if a high clinical suspicion was present. In patients with ACR and concomitant PTLD, capsule endoscopy was used to evaluate treatment response to enable further modification of the immunosuppression (**Figure 10**). The international algorithms for gastrointestinal bleeding were similarly applicable in this cohort, when suspicions of the latter arose (117, 118). The use of video capsule endoscopy for detecting PTLD was however only considered if there was a high suspicion and if no other foci had been located, or to examine a lesion with a probable location in the small intestine.

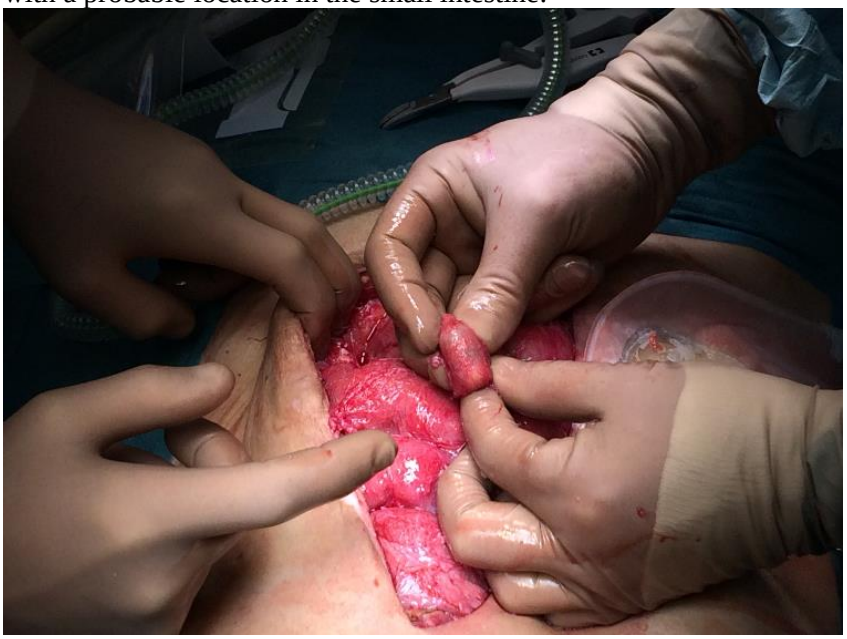

Figure 10: A video capsule retained in the small intestine.

3.2.6 GOTHENBURG INTESTINAL TRANSPLANT ENDOSCOPY SCORE (STUDY IV)

The endoscopic findings during an episode of ACR have previously been described and include non-specific mucosal findings such as erythema, friability, granularity or ulceration (106). These abnormalities progress as the ACR worsens. We therefore applied these features in a five-stage endoscopic score similar to the Mayo score, which is used for describing colonic features in ulcerative colitis (119). Our aim was to develop a straightforward score for describing and categorizing findings in the small intestine after intestinal transplantation (**Figure 11**). Additionally, calprotectin was measured in conjunction to some of the endoscopy sessions, and the value of this test was also assessed.

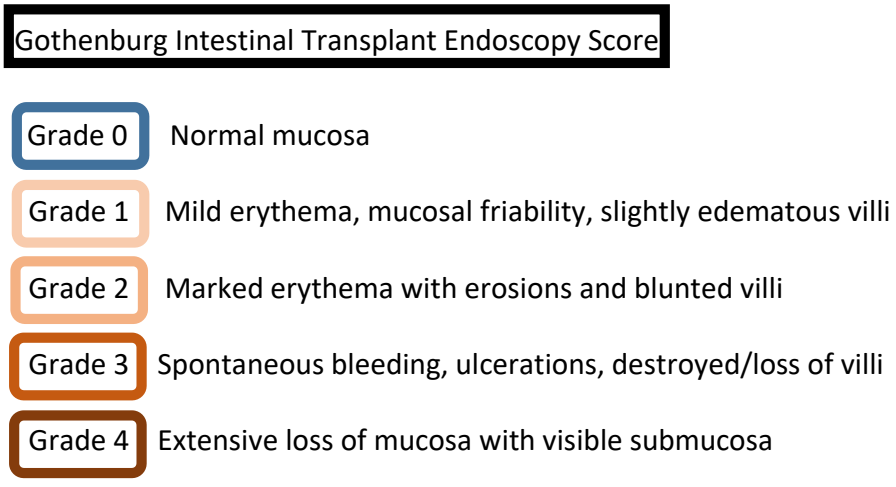

Figure 11. The newly developed Gothenburg Intestinal Transplant Endoscopy Score and the different grades used in this score.

3.3 STATISTICS

Considering the small patient cohorts in these studies due to the rarity of these conditions, along with a heterogeneous population and only a few transplants being performed, the use of statistical methods were predominantly focused on descriptive statistics, expressed as median and range for continuous data and frequencies and percentages for categorical variables (Study I- IV). Fisher Exact test was also used to assess differences in ACR rates between groups (Study II). The endoscopy sessions were all interpreted individually and not on a patient-by-patient basis in study IV.

Kaplan-Meier survival analysis was used with the log-rank test for the comparison of patient survival lengths between the different groups (Study I & II).

For the agreement between the two methods either Cohen´s kappa analysis (Paper I) or weighted Cohen´s kappa analysis was used (Paper IV). The concordance between the two investigators were estimated in paper IV. Specificity, sensitivity, positive predictive value, and negative predictive value were also calculated for the new scoring system in paper IV.

4 RESULTS AND DISCUSSION

This section highlights the key results obtained in the four manuscripts and discusses the findings in comparison with relevant studies from the existing literature.

4.1 STUDY I AND II

Study I described the survival of patients that were referred for transplantation. Each patient was further assigned to groups depending on the management strategy decided by the multidisciplinary team and these subgroups were thereafter compared. Study II focused on transplanted patients and outcome measures such as immunological complications, nutritional outcome, and survival **(Figure 12)**.

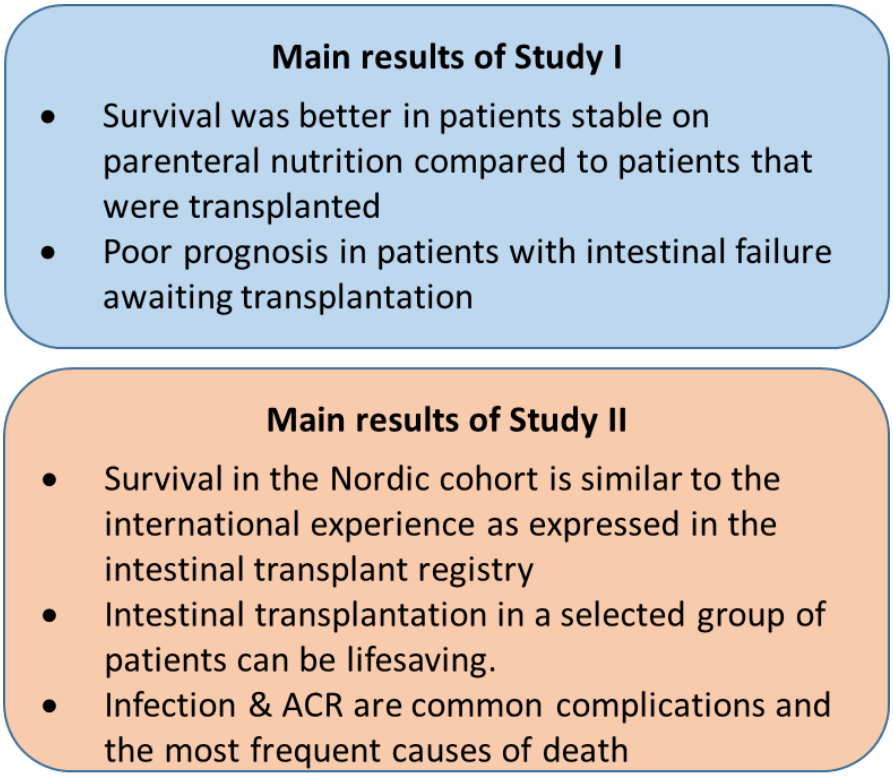

Figure 12. Main results of Study I & II.

4.1.1 INDICATIONS FOR TRANSPLANTATION

The underlying etiology precipitating the subsequent need for transplantation differed when comparing our cohort with the registry data (**Table 2**). The indications *per se* followed the recommended guidelines, but our group comprised of a significantly higher proportion of patients with neuroendocrine pancreatic tumours.

Our data also suggested that a different strategy would be feasible when listing paediatric patients as compared to adults. In general, the guidelines that were formed in 2001 (99) have been used in most countries and also at our centre. However, reports have questioned some of these indications, such as the grading of the severity of sepsis, but confirmed the importance of other factors such as thrombosis, liver failure and invasive desmoid tumours (100, 120). Moreover, the evolution of treatment strategies in medicine (e.g. fish oil based emulsions, GLP-2 analogues, taurolidine lock), surgery (e.g. autologous gastrointestinal reconstruction, mesenteric stroke units, bowel lengthening procedures) and interventional radiology have resulted in reversal of some complications previously destined for transplantation. Therefore, the importance to adopt these treatment strategies becomes essential for optimizing the care given to each individual. (52, 67, 121, 122).

Nevertheless, transplantation remains an excellent strategy in patients who have exhausted standardized therapeutic options and who fulfils the indications for transplantation. Other non-standard indications, such as diffuse mesenteric vein thrombosis, desmoid tumours and abdominal catastrophes either causing mesenteric vessel injury or frozen abdomen, may potentially become more prevalent in the near future.

Another factor that has been thoroughly discussed is the role of poor quality of life as an indication for intestinal transplantation. It appears that the quality of life in both adults and children can improve following transplantation, but the risk/benefit ratio needs to be assessed thoroughly, bearing in mind that the existing studies assessing quality of life after transplantation are limited in numbers and scope (123).

	Referred Tx Europe		**Referred Tx Gothenburg**		**Transplanted Nordic**		Transplanted World	
Time period			1998-2009		1998-2013		1986-2018	
	Adults	Peds	Adults	Peds	Adults	Peds	Adults	Peds
No of subjects	688	166	43	19	22	12	1545	1857
Centres	33	8	1	1	4	4	71	68
Female	57%	48%	63%	58%	55%	83%	50%	44%
Age	53 y	6 y	44 y	7 y	42 y	6 y	40 y	2.5 y
Etiology								
Short gut	75%	52%	37%	21%	23%	8%	59%	60%
Motility disorder	18%	23%	21%	37%	23%	68%	11%	19%
Mucosal defect	1%	15%		26%		16%		9%
Retransplantation					(5%)		17%	11%
Tumours	2.5%		28%		31%	8%	13%	1%
Mesenteric ischemia	(36%)				18%			
Other	3.5%	10%	14%	16%	5%			
Survival			*	*	#		¤	¤
1 year	96%	100 %	73%	64%	79%	92%	62-80%	78-83%
3 year	90%	94%	55%	64%	62%	92%	47-69%	64-73%
5 year	84%	90%	55%	64%	62%	92%	21-69%	57-64%
Causes of death			*	*			¤¤	¤¤
No of subjects	55	8	13	5	11	1	345	285
Disease/ Comorb	25%	50%	31%					
IF related	30%	40%	54%	100%				
Unrelated	45%	10%	15%		9%			
Transplant related								
Tumour recurrence					18%			
Rejection/infection					65%		46%	53%
PTLD					9%	100%	6%	7%
Graft associated							12%	12%
Other							36%	28%

*Table 2. Comparison of results of study I & II with results from a European multicentre study (124) and with data acquired from the intestinal transplant registry (125). *indicates that all patients who underwent intestinal transplantation are excluded from the analysis. # indicates that the survival analysis in the adult patients are based on data from 2003-2013. Among the patients transplanted across the world, the survival analysis includes the period 2009-2015¤, and the mortality data is derived from patients transplanted after 2006 ¤¤. One patient was re-transplanted, as indicated above. The indication for her first procedure is already recorded. Therefore, the indication for the second graft is placed within brackets.*

4.1.2 TRENDS IN REFERRAL PATTERNS

The number of patients being referred to our transplant unit has gradually increased over the years even though the rate of actual transplants has remained constant, indirectly highlighting the importance of multidisciplinary evaluation and the application of alternative treatment strategies. Similarly, these findings indicate an increased awareness of the transplant procedure and the importance for seeking second opinion. Nonetheless, many patients were referred to us at an advanced stage with multiple complications, necessitating the need for a liver containing graft, which is in contrast with the global experience. Furthermore, internationally most of the transplants were done in North America 74% (n=2640) followed by Europe 21% (n=740), Latin America 3% (n=110) and Asia/Australia 3% (n=100), where the dominant part of these procedures were performed in only 10 centres. Moreover, the trend of annual caseloads showed a declining trajectory with a peak observed in 2008, although a bias exists due to the relative decline in the reported cases to the registry. In spite of the addition of the United Network of Organ Sharing (UNOS) data to compensate for this deficit, a gradual decline is still seen although a second peak was observed in 2016 (125).

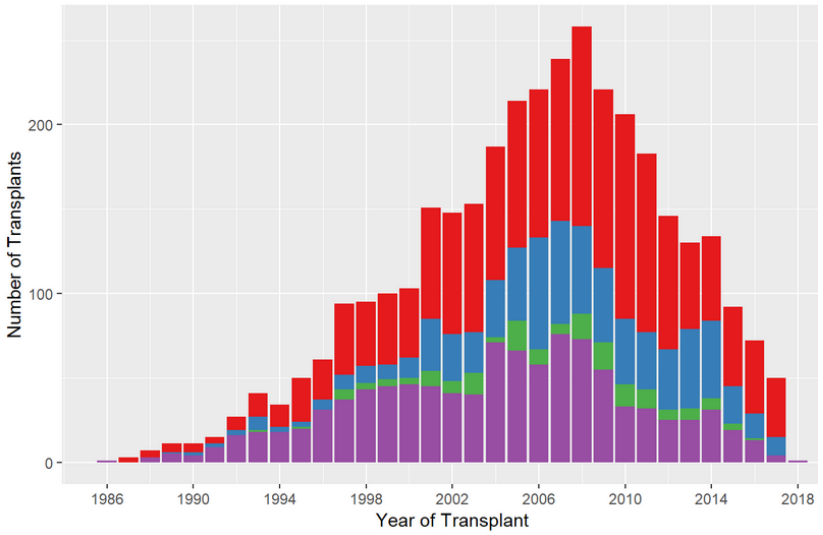

Figure 13. The cumulative caseload of all transplantations performed worldwide and registered in the International transplant registry. Data obtained with permission from the Intestinal transplant registry (125). *Isolated intestinal transplantation* *Multivisceral transplantation* *Modified multivisceral transplantation* *Liver-small bowel transplantation*

4.1.3 GRAFT CONSIDERATIONS

The type of intestinal graft chosen for our patients depended on factors mentioned previously. The rationale of primarily having liver containing grafts can be explained by late referrals e.g. established IFALD at assessment for transplantation but also due to a high proportion of patients with malignant disease (n=8: Neuroendocrine pancreatic tumours, desmoid tumours, pancreatoblastoma). These results are in contrast with the trend observed globally i.e. grafts with predominantly isolated intestines (125). Paradoxically, this may lead to an impaired graft survival since the inclusion of a liver component itself is related to a significantly better graft survival (HR 0.72, $p< 0.017$) (126). Some centres are even obliged to wait until the criteria to include a liver graft is met. Moreover, a survival benefit has also been noted by including a liver graft in any patient who has lost their first intestinal graft. These strategies must adhere to an overall fair allocation process for isolated liver or multivisceral (liver-containing) grafts alike (127).

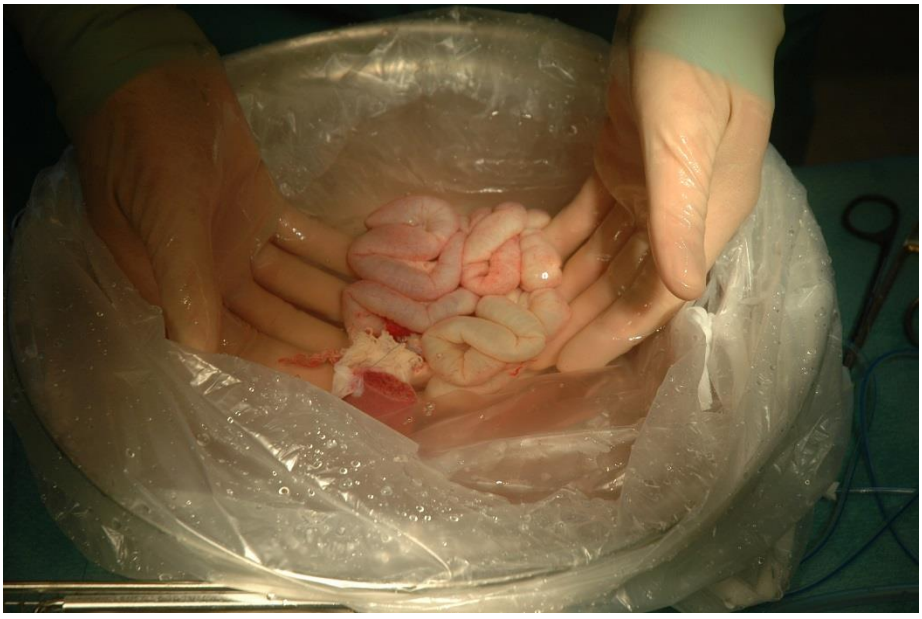

Figure 14. An isolated paediatric intestinal graft during "backtable" preparation prior to transplantation.

4.1.4 IMMUNOLOGICAL COMPLICATIONS

The immunological challenges posed by the transplanted graft were reflected in our cohort with a high proportion of ACR, GVHD and PTLD, well in line with the international experience (**Table 3**).

ACR was frequently encountered, with most cases arising during the first three months after transplantation. Graft failure did occur as a consequence of rejection (ACR, n=3, Chronic rejection, n=2), but only so in patients with isolated intestines (1-13 years after the initial transplantation). Overall graft survival in patients receiving isolated intestines seemed to be worse compared to liver containing grafts (5-year survival 60% vs. 68% and 10- year survival 40% vs. 57% for isolated intestine and multivisceral grafts, respectively) in the Gothenburg cohort (1998-2021). This experience is similar to the global experience where graft failures are less frequent in patients with liver and small intestinal grafts (65-66% 5-year survival) compared to intestinal grafts alone (41-48%). In total, the frequency of ACR was higher in our cohort (70-74% in adults and paediatric patients, respectively) compared to the global experience for either isolated intestinal grafts in children (58%) or liver containing grafts in adults (29%) (22, 128). The higher proportion of ACR seen in our cohort might in part be due to the definition of rejection we adhered to (as histologic grades of indeterminate for ACR were included), and potentially to the presence of false positive cases because of the difficulties in differentiation from viral etiology (prior to the availability of specific staining techniques), along with a longer follow-up time.

GVHD developed with an acute onset in the early weeks after transplantation and manifestations included skin rash on the torso and hematologic manifestations. The relatively high frequency of GVHD that we experienced might consequently be due to the high proportion of patients with malignant disease since the majority of patients presenting with GVHD also had a history of chemotherapy prior to their transplantation which may have rendered them more susceptible to the immunological load of donor cells.

	Transplanted Nordic		**Transplanted World**	
	Adults	Pediatric	Adults	Pediatric
Graft type				
Intestine	5	7	988	739
+ Liver	18	5	557	1118
Complications				
ACR	74%	70%	33% ##	55% ##
PTLD	4%	33%	6%**	21%**
GVHD	17%	8%	5%**	13%**
Nutritional autonomy	*75% (9/12)	*67% (6/9)	61%	57-75%¤
Survival*				
1 year: Intestine	100%	86%	80%	83%
1 year: +Liver	66%	100%	62-80%	78%
5 year: Intestine	#	86%	61%	64%
5 year: +Liver	54%	100%	21-69%	57-62%

*Table 3. Summary of different outcome measures from the Nordic cohort compared with international registry data (125),## Scientific registry of transplant recipients (22, 128), and data from ** the University of Pittsburgh Medical centre (13). Liver-containing grafts included both patients with multivisceral grafts and intestine with liver. Intestine with liver is depicted with the higher survival rate within the range and multivisceral transplantation with the lower survival rates. * Nutritional autonomy was defined as being weaned off parenteral nutrition 12 months after the transplantation. ¤ Improved autonomy was also seen in children receiving an additional colon graft. # Insufficient cases to calculate long-term survival.*

4.1.5 SURVIVAL IN PATIENTS REFERRED FOR TRANSPLANTATION

The survival of each patient was dependent on how each person was classified at the time of the evaluation with a trend for a superior survival in the following order:

No indications for transplantation > Patients who were stable on PN > Accepted for transplantation > Contraindications for transplantation.

On further subgrouping, a higher mortality was observed among patients on the waiting list who did not receive a graft (2/4 adults, 4/6 children died), when compared to patients who were accepted and underwent transplantation. These findings highlight the superior survival in patients stable on parenteral nutrition in comparison to those being transplanted. The presence of life-threatening complications led to a poorer prognosis, showing the complexity of this patient group and the importance of accurate selection for transplantation.

Unfortunately, organ scarcity remains a detrimental factor and this is illustrated by a lengthy waiting list period. Similar patterns were seen in the Scientific Registry of Transplant Recipients and measures like earlier referral and prioritization on the organ allocation list may affect these outcomes. Correspondingly, the risk of death among adult candidates awaiting liver containing grafts (multivisceral, intestine-liver) was twice than that in liver transplantation. For this reason, a modified allocation system was implemented in the US to prioritize this cohort, matching that what was done in Europe and Latin America, where liver-intestine transplantation is placed just below the most critically ill patients (22, 127). Similarly, a joint Nordic waiting list was implemented in 2013 for children waiting for isolated liver transplantation and for adults and children waiting for intestinal transplantation (129).

Along these lines, in our cohort the cause of death among patients who required PN was most often related to intestinal failure/ PN, followed by their primary illness, which is in contrast to the transplanted patients, who primarily died of transplant-related factors. These findings mimic the international experience and show how one set of impending complications is exchanged for another set following transplantation (120, 125). Nevertheless, this fact needs to be relativized, since many of these patients undergo transplantation as a last resort to save their lives.

4.2 STUDY III AND IV

Study III investigates a new approach to depict pathology arising in the transplanted graft. Each indication is grouped separately, and the findings are compared to histology. In Study IV a new endoscopic grading score was constructed, and its reliability was assessed. The main results of manuscript III and IV are presented in **Figure 15**.

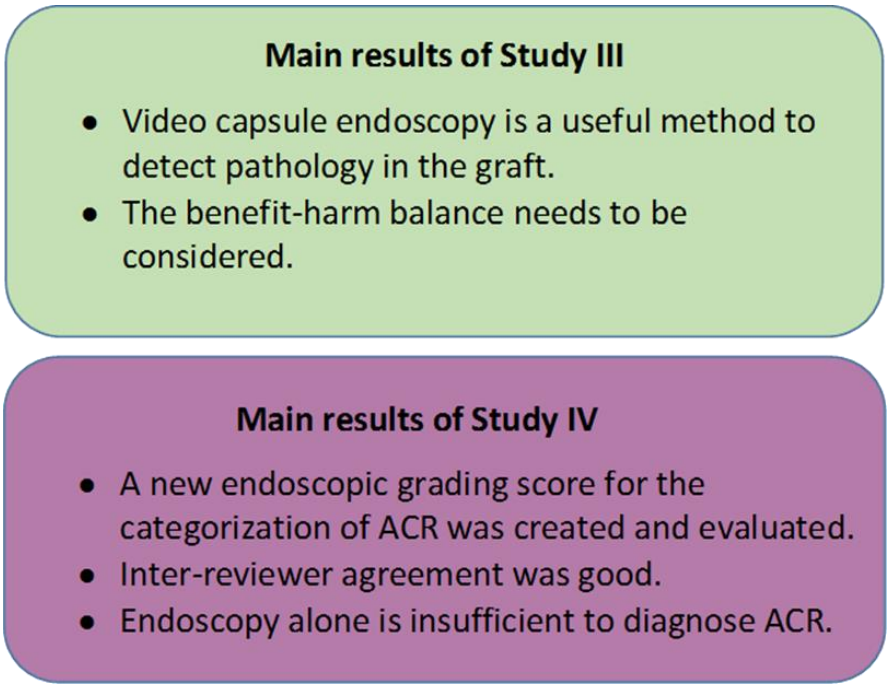

Figure 15. The main result of study III and study IV.

4.2.1 VIDEO CAPSULE ENDOSCOPY

The complexity in visualizing the entirety of the intestinal mucosa and the relevance of detecting pathologic features here is unknown. Consensus exists regarding the importance of detecting immunological complications, e.g. ACR, at an early stage and thereafter instigating prompt treatment. The strategy on how to best achieve this is flawed due to the invasive nature of the endoscope and the fact that only 10% of the mucosa can be visualized.

The additional value with video capsule endoscopy was around 80% in our experience and rendered either assurance for the clinician, surgical intervention, adjustment of immunosuppression or identification of lesions potentially inducing the symptoms (**Figure 16**). Similarly, an abstract from a multicentre study included 33 examinations and showed a benefit in 73% with alterations in the management strategies in 19% of the cases (130). The most commonly observed pathology in our cohort was ACR with clinical manifestations ranging from abdominal discomfort to a more fulminant course. These findings are in line with previous conclusions highlighting the difficulties in identifying a clear correlation between specific symptoms and ACR, thus emphasizing the need to investigate these patients thoroughly (131). However, the importance to visualize the entirety of the gastrointestinal tract cannot be answered from this study alone, as features observed outside the reach of the endoscope most often also appeared within its range, making rejection in an isolated mid intestinal segment less likely.

Adverse effects such as capsule retention and obstruction also need to be addressed, especially since the investigation is performed in patients with risk factors including altered anatomy, use of opioids and acute illness. Each of these factors can predispose for complications, which was reflected by the fact that most examinations had a delayed passage time and 17% were retained, which is high when compared to various other gastrointestinal conditions (gastrointestinal bleeding 1.2%, Crohn´s disease 2.6% and neoplastic lesions 2.1%) (132), but mimics the finding in other patients who underwent intestinal transplantation (111). Furthermore, the risk of having an incomplete examination and the fact that biopsies cannot be obtained during the session also restricts this technique from a more widespread use.

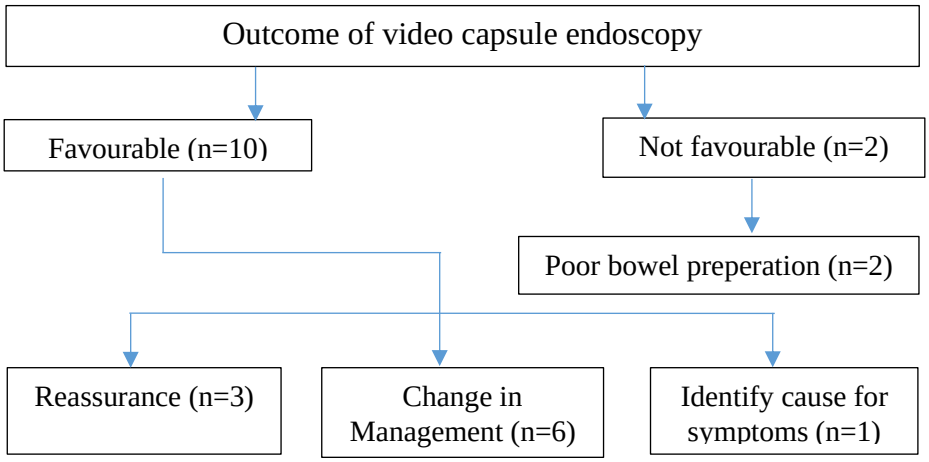

Figure 16. This flowchart illustrates the outcome of each examination. "Change in management" included alterations in immunosuppression (n=5) or graft enterectomy (n=1).

4.2.2 GOTHENBURG INTESTINAL TRANSPLANT ENDOSCOPY SCORE

The Gothenburg intestinal transplant endoscopy score was constructed to bridge the current gap of inconsistent reporting of endoscopic findings to a more standardized model. The simplicity of the system resulted in a superb inter-observer agreement but only moderate agreement between histology and endoscopy. However, the correlation to histology did improve when using high definition endoscopy systems and when more advanced stages of ACR were present. The difficulties in detecting early stages of ACR (**Figure 17**) and relying on visual inspection alone have been identified before. The Pittsburgh group has shown that 6% of rejections in asymptomatic and 25% in symptomatic patients would have been missed with this strategy alone. This issue was further addressed by the Miami group as they evaluated the benefits of zoom endoscopy, showing that most patients identified as healthy during the endoscopy also had negative biopsies. However, difficulties in identifying patients with ACR was a limiting factor with this system. Correspondingly, the scoring system used by the Miami group has not been adopted due to its complexity (133). The advantages with zoom endoscopy over video endoscopy has also been questioned by the Pittsburgh group (134) (**Table 4**).

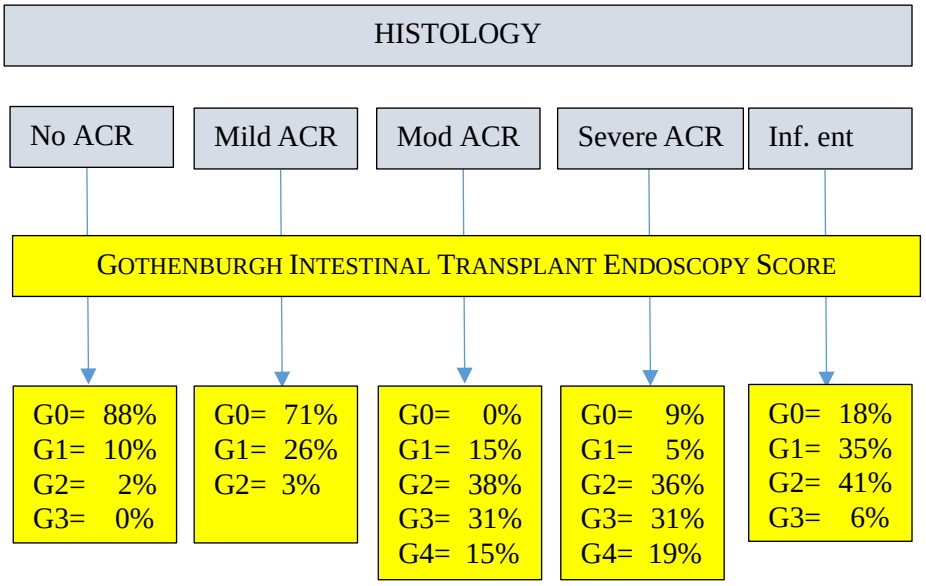

Figure 17. Dispersion of endoscopic findings according to the GITES score. G0= Normal, G4=Extensive mucosal loss, visible submucosa.

Moreover, the pitfall of exclusively relying on histology is a risk that needs to be addressed, especially if there is discordance between endoscopy and histology. Infections such as gastrointestinal CMV (seen in 16-24% of all patients), clostridium difficile (20%) and other viral enteritis (adenovirus, rotavirus, norovirus: 44%) are conditions that frequently present in the transplanted patients and often necessitate endoscopy. Histopathologic findings here could similarly include apoptotic bodies, despite the absence of ACR. To further complicate this matter, 15-67% of patients with a viral enteritis also develop ACR either simultaneously or in the recovery phase of the infection. The importance of having experienced pathologists and a multidisciplinary approach to diagnose ACR has therefore been highlighted (33, 109).

Modality	Sensitivity	Specificity	PPV	NPV
Zoom Endoscopy				
Miami 2005 (133)(n=499)	52%	93%	67%	87%
¤Bologna 2008 (135)(n=270)		95%		
*Bologna 2014 (136)(n=52)		98%		
Endoscopy				
Pittsburgh (137)1998 (n=1273)	63%			
Pittsburgh (134)2012 (n=1024)	45%	79%	55%	79%
California 2016 (138)(n=1770)	55%			
Gothenburg 2018 (n= 512)	**69%**	**83%**	**50%**	**92%**

Table 4. Correlation between endoscopy and histology in different studies. ¤ *Not clear if specificity is related to pathologic finding or ACR*
**No cases of ACR and very few cases with pathologic findings (n=8).*

4.2.3 BIOMARKERS

Faecal calprotectin has shown to be valuable in excluding intestinal pathology, but regrettably any type of pathology causing inflammation could result in elevated levels (139). Our model included a combination of faecal calprotectin and endoscopic findings in a subset of patients. This strategy improved the interpretation of the macroscopic findings, since endoscopic findings in conjunction with high calprotectin levels were more plausibly related to rejection, but other causes cannot be totally excluded (e.g. infectious enteritis).

The use of calprotectin may also be indicated in clinical scenarios where endoscopy is problematic in asymptomatic patients or when a high calprotectin level is noted in a patient with a normal lower endoscopy, thus directing the clinician to perform further investigations. Other markers that have been suggested to be of potential value are gut microbiota (140) or non-HLA antibodies (141). The usefulness of these markers needs to be investigated in larger studies prior to reaching clinical practice.

4.3 LIMITATIONS

These studies have several limitations primarily due to the retrospective nature of all the studies, and the fact that they are composed of a small and heterogeneous patient cohort including both adults and children with benign and malignant etiologies. These factors combined should be taken into account as they limit the type of statistical conclusions one can draw from these results. Moreover, in this thesis several comparisons were made between our data and international registry data. However, there are several biases that needs to be addressed while interpreting registry data. A significant selection bias and information bias can be expected, e.g. underestimation of true disease states due to the inability to capture subclinical cases, differences between participants and non-participants, information bias due to inadequate methods and/or quality of data collection, measurement error and missing data.

5 CONCLUSION

- Patient selection is crucial when identifying individuals that would benefit the most from intestinal transplantation. Moreover, PN has shown to be superior to transplantation in patients who are stable on PN. Similarly, the procedure can be lifesaving when patients are selected adequately.

- Patients transplanted from the Nordic region did achieve survival rates comparable to international standards, which legitimizes the continuing practice at these centres.

- Intestinal transplantation is a procedure afflicted with a multitude of complications, but the procedure may still be warranted when facing a patient with life threatening complications of PN or other underlying primary disease.

- Video capsule endoscopy has a potential role in the investigation of graft complications, especially when other modalities fail to provide sufficient information. Furthermore, the risk of this investigation needs to be thoroughly acknowledged beforehand, as the risk for potential harm is higher in this group of patients.

- A new endoscopic grading score was evaluated and showed an excellent inter-rater agreement. The study further confirmed the inability of visual impression to reliably diagnose ACR on its own.

6 GENERAL DISCUSSION AND FUTURE PERSPECTIVES

The field of intestinal failure has dramatically evolved over the last decade with the widespread implementation of innovative strategies in the field of medicine, surgery, and interventional radiology at intestinal failure centres. These efforts have collectively improved the outcome of this cohort resulting in fewer life-threatening complications and thus fewer referrals to transplantation.

Nevertheless, intestinal transplantation continues to have a crucial role among patients with life-threatening complications of PN. Additionally, other territories have also been explored with satisfactory outcomes e.g. patients with advanced portomesenteric vein thrombosis and when desmoid tumours compresses the mesenteric root. Therefore, the importance of having a dynamic approach to listing is essential, basing each decision on the most optimal strategy available for each patient.

Expanding the indications by including poor quality of life in intestinal failure patients as the primary reason for transplantation has previously been debated. This strategy is highly questionable in its making due to a substantial risk of succumbing to immunological complications e.g. ACR. However, this approach might be acceptable if immunosuppressive strategies were developed resulting in improved graft tolerance and consequently fewer complications. Until this goal is achieved, our efforts should also be directed towards improving our diagnostic modalities for early detection and treatment of ACR.

The optimal strategy for monitoring the graft would have been a biomarker, but current options are insufficient and their use in clinical practice varies. Cross-sectional imaging, such as CT and MRI, have been reported during episodes of ACR (142-146). These modalities provide an additive effect by detecting the consequences of rejection but the possibility to detect early signs of ACR is less likely. Similarly, the use of intestinal ultrasound has an appealing approach with the possibility of visualizing a large portion of the small bowel in real-time and thereby assessing inflammation and its corresponding consequences. This method is now common practise in the field of inflammatory bowel disease but needs further validation for the transplanted graft (147). Moreover, endoscopic ultrasound might offer additional information, providing accurate measurements of wall thickness and vascularization of a limited segment of the bowel, but its role in diagnosing complications e.g. ACR or chronic rejection remains unproven. Perhaps,

improving the endoscopic approach might be a feasible option to improve the quality of the examination. A first step is to standardize the visual appearance with e.g. GITES, and to implement and evaluate this score in a multicentre trial. To further improve this strategy and compensate for the shortcomings of visual impression to diagnose ACR, the use of artificial intelligence (AI) using deep learning (148, 149) likely results in the possibility of acquiring targeted biopsies and improved detection rate with a smaller inter-rater variability. Furthermore, endocytoscopy utilizing a magnification of >500-fold would be another potential improvement, especially if this is combined with AI, making the use of histopathology unnecessary. AI and endocytoscopy has currently reached the field of gastroenterology, focusing on the detection and characterization of colonic polyps alone (150-153). Most likely, these systems will revolutionize the field of gastroenterology, but the question remains if the industry will develop these systems for application in graft surveillance. The collaborative efforts of the multidisciplinary team will still be essential since the diagnosis of the condition requires a holistic evaluation.

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