# Intestinal Transplantation as a management of Intestinal Failure

**Essay**
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بسم الله الرحمن الرحيم

وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ
ورَسُولُهُ والْمُؤْمِنُونَ

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*Mahmoud Shedeed*

# *List of Contents*

# List of Abbreviations

| | |
|---|---|
| APC | Antigen Presenting Cells |
| BG | Blood Glucose |
| CBC | Complete Blood Count |
| CHF | Congestive Heart Failure |
| CMV | Cytomegalovirus |
| CIT | Cold Ischeamia Time |
| CIPO | Chronic Intestinal Pseudo-Obstruction |
| CRS | Catheter related sepsis |
| Cu | Cupper |
| CVC | Central Venous Catheter |
| CVT | Central Venous Thrombosis |
| EBV | Epestien Barr Virus |
| EGD | Esophagogastrodudenoscopy |
| EGF | Epidermal Growth Factor |
| GH | Growth Hormone |
| GrB | Granzyme B |
| GVHD | GraftVersus Host Disease |
| HBV | Hepatits B Virus |
| HCV | Hepatitis C Virus |
| HLA | Human Leucocyte Anigen |
| IF | Intestinal Failure |
| IFALD | Intestinal Failure Associated Liver Disease |
| IGF-1 | Insulin like Growth Factor-1 |
| IMA | Inferior Mesenric Artery |
| IMV | Inferior Mesenric Vein |
| ITx | Intestinal Transplantation |
| IVC | Inferior Vena Cava |
| KGF | Keratinocyte Growth Factor |
| LCT | Long chain Triglycrides |
| LD | Living Donor |
| LDF | Laser Doppler Flowmetry |
| LDITx | Living Donor Intestinal Transplantation |

# List of Abbreviations (Cont. )

| | |
|---|---|
| LR-SBTx | Living Related Small Bowel Transplantation |
| MCT | Moderate chain Triglycrides |
| PACU | Post Anasthesia Control Unit |
| PE | Pulmonary Embolism |
| PT | Prothrombin Time |
| PTLDS | Posttransplantlymphoproliferative Disorders |
| S. aureus | Staphylococcus Aureus |
| SBS | Short Bowl Syndrome |
| SMA | Superior Mesenric Artery |
| SMV | Superior Mesentric Vein |
| SRL | Sirolimus |
| TAC | Tacrolimus |
| TGF a | Transforming Growth Factor a |
| TPN | Total parentral Nutrition |
| Zn | Zinc |

# List of Figures

# List of Tables

# Introduction

Short bowel syndrome is the label commonly applied to most patients with intestinal failure. However, the term *intestinal failure* is preferred, and it is the more descriptive, functional term **(O'Keefe et al., 2007)**. Short Bowel Synrome is defined as the malabsorptive state, which follows massive small bowel resection. This syndrome occurs when there is <200 cm of residual bowel. Intestinal Failure is defined as a reduction in the functioning of gut mass below the minimum amount necessary for adequate digestion and absorption of nutrients to achieve and maintain normal nutritional status **(Fleming, 1981)**.

Most data on intestinal adaptation after extensive small bowel resection come from animal studies **(Thiesen et al., 2003)**. Although different species can tolerate different degrees of resection, the ability to survive free of parenteral nutritional support following intestinal resection depends on the magnitude of residual functional intestinal capacity, compensatory mechanisms, and the adaptive restitution. Evidence for functional adaptation in humans includes the observation that parenteral fluid and electrolyte requirements decline with time and many patients are able to be weaned off parenteral nutrition **(Alan Langnas, 2012)**.

Patients with Intstinal Failure are kept on TPN for long periods, long term TPN has multiple adverse effects, which concern numerous systems and organs. Biliary complications are rather common because of the decreased oral intake of food, which contributes to decreased gallbladder motility and development of sludge and gallstones **(Ling et al., 2001)**.

Liver complications are also common in patients dependent on TPN. Steatosis, sometimes combined with

hepatitis, cholestatic liver disease, fibrosis and even cirrhosis can be observed in these patients **(Buchman et al., 2001)**.

The most frequent indication for intestinal transplantation is progressive liver disease associated with parenteral nutrition therapy and disuse of the gastrointestinal tract, i. e. ; TPN associated cholestasis **(Brown et al., 2004)**.

In 1988 Deltz and coworkers in Kiel, Germany, performed what is considered to be the first successful intestinal transplant **(De Serre et al., 2012)**. Soon after, other successful outcomes were reported by the groups headed by Goulet and coworkers in Paris **(Goulet et al., 1990)** and Grant and coworkers in London, Canada, who had established the first intestinal transplant programs **(Grant et al., 2005)**.

Among abdominal organ transplants, intestinal transplantation has always had a poor reputation because of its inferior outcome relative to liver, kidney, and pancreas grafting **(Brown et al., 2004)**.

# Aim of The Work

The aim of this work is to discuss Intestinal Transplantation as a management of Intestinal Failure

# Historical Background

The beginning of the 21st century has ushered in almost 15 years of success with the clinical transplantation of intestine, however, this has come after 40 years of elusive success and frequent setbacks **(Reyes et al., 2007)**.

Experimental models of the procedure were developed in the late 1950's and early 1960's before the introduction of TPN , at that time, patients with short bowel syndrome were doomed to die within a short time **(Lillehei et al., 1959)**.

The development of total parenteral nutrition (TPN) by Wilmore and Dudrick in 1968 **(Dudrick et al., 1968)** and long-term intravascular central lines by Broviac in 1972 **(Broviac et al., 1974)** enabled dramatic change in the prognosis of patients with intestinal failure. Consequently, the intestinal transplantation had to wait, not only for the development of solid platforms of multi-organ transplantation, but also, most importantly, for a better understanding of immunosuppression and the immunologic event that had led to success with other organs. These historic strides have followed three intimately related paths; surgical techniques and then development of intestinal grafts and their various forms and finally the evolution of immunosuppressive management. Interests in intestinal transplantation waited until 1980's after the side effects and limitations of TPN became apparent and cyclosporine was successfully used for other organ transplantation **(McAlister et al., 1994)** .

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and coworkers in London, Canada, who had established the first intestinal transplant programs **(Grant et al., 2005).**

Finally, the introduction of the new antirejection agent tacrolimus in 1989 changed the transplant landscape, allowing for intestinal transplantation to evolve into a widely performed and successful transplant.

The first LD intestinal transplant in Tacrolimus era was reported by Morris et al., in 1995; a 31 years old man with desmoid tumor underwent excision of the tumor, and in the same session a small bowel transplant from his mono zygotic twin **(Morris et al., 1995) .**

While avoiding rejection. Another adverse effect of heavy immunosuppresion appeared to be a substantial increase in the incidence of chronic rejection **(Starzl et al., 2004).**

The near total loss of progressive tolerance that had allowed low dose maintenance immunosuppresion or immunosuppresion free management in a proportion of the earlier procedures. A possible explanation for the divergent frequencies of acute and chronic rejection and the potential key to tolerance with minimal immunosuppresion came from the report by (Starzl et al., 1992) in the 1$^{st}$ half of 1990s that long term tolerance was associated with donor and host leucocyte chimerism **(Starzl et al., 1992)**.

Judicious immunosuppresion with the aim of engaging graft and host in a manner that encourages tolerance with minimal immunosuppresion has become the goal of modern transplantation immunosuppresion.

Today, treatment principles for induction of transplant tolerance continue to evolve. A group of strategies collectively known as "immune modulation" is currently undergoing clinical trial with all major organs, including intestine.

Although rejection remains an important post transplantation risk, GVHD has been less of a clinical problem than initially feared. Thanks to refined medication and patient selection strategies along with the use of bone marrow augmentation, one and five year adult rates are reported at 72 percent and 50 percent respectively **(Barr et al., 2003)**.

In 1997, report of the International Registry for Intestinal Transplantation stated that intestinal transplantation had become a lifesaving procedure for patients with intestinal failure who could not be maintained on total parenteral nutrition (TPN). The report further stated that intestinal transplantations performed since 1991 at centers performing more than 10 intestinal transplantations per year had significantly higher graft survival rates **(Grant et al., 1999)**.

As of May 2003, a total of 989 transplants were registered at the International Intestinal Transplant Registry (children and adults) **(Fryer, 2005)**.

Now intestinal transplant has become the treatment of choice for patients with end stage intestinal failure and life threatening complications on TPN. With over 40 centers in North America and over 60 worldwide that has performed this challenging procedure **(Barr et al., 2006)**.

# Anatomy of Small Intestine and physiology of adaptation

The normal human small intestinal length from the duodeno-jejunal flexure to the ileocaecal valve as measured at autopsy, by a small bowel enema or at surgery varies from about 275 to 850 cm and is shorter in women. The full intestinal length is achieved by 10 years of age **(Bryant, 1924)**.

Radiological measurements of small bowel length give shorter results than those obtained at autopsy or surgery, partly because radiographs are only in two dimensions. A small bowel enema causes bowel distension leading to overall shortening **(Fannucci et al., 1988)**.

The bowel may also be apparently shortened when measurements are made after passing a small flexible polyvinyl plastic tube through the nose to the caecum as this causes the bowel to telescope around the tube **(Slater & Aufses, 1991)**.

An appreciation of the wide range of normal small intestinal length is important and emphasizes the need, after a bowel resection, to refer to the remaining length of small intestine rather than to the amount resected **(Nightingale & Spiller, 2001)**.